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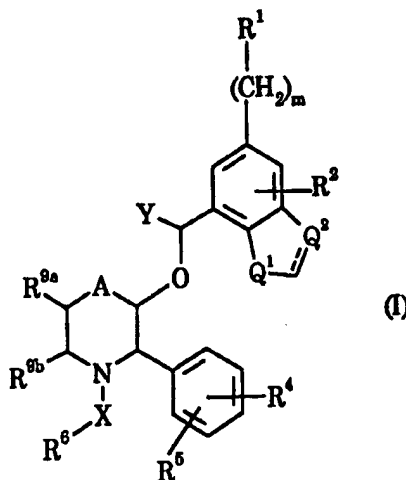
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| (21) International Application Number: PCT/GB96/01477 (22) International Filing Date: 20 June 1996 (20.06.96) (30) Priority Data: 9513121.5 28 June 1995 (28.06.95) GB (71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BAKER, Raymond [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). ELLIOTT, Jason [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). STEVENSON, Graeme, Irvine [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). SWAIN, Christopher, John [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). (74) Agent: HISCOCK, Ian, James; Merck & Co., Inc., European Patent Dept., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). | | (81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. |

(54) Title: PIPERIDINE AND MORPHOLINE DERIVATIVES AND THEIR USE AS THERAPEUTIC AGENTS

(57) Abstract

The present invention provides compounds of formula (I), wherein R¹ is phenyl or a 5- or 6-membered aromatic heterocyclic group containing 1, 2, 3 or 4 heteroatoms, selected from nitrogen, oxygen and sulphur, which aryl or heteroaryl group is optionally substituted; R² is hydrogen, halogen, C₁-alkyl, C₁-alkoxy, CF₃, OCF₃, NO₂, CN, SR^a, SOR^a, SO₂R^a, CO₂R^a, CONR^aR^b, C₂-alkenyl, C₂-alkynyl or C₁-alkyl substituted by C₁-alkoxy, where R^a and R^b each independently represent hydrogen or C₁-alkyl; R⁴, R⁵, R⁶, R^{9a} and R^{9b}, A, X, and Y are as defined in the specification; the dotted line is an optional double bond; Q¹ is oxygen, sulphur or -NH-; Q² is -N=, -NH-, -CH= or -CH₂-; and m is zero or 1; and pharmaceutically acceptable salts and prodrugs thereof. The compounds are of particular use in the treatment or prevention of pain, inflammation, migraine, emesis and postherpetic neuralgia.



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PIPERIDINE AND MORPHOLINE DERIVATIVES AND THEIR
USE AS THERAPEUTIC AGENTS

This invention relates to a class of aromatic compounds which are
5 useful as tachykinin antagonists. More particularly, the compounds of the
invention contain an amine-substituted azo-heterocyclic moiety.

The tachykinins are a group of naturally occurring peptides found
widely distributed throughout mammalian tissues, both within the central
nervous system and in peripheral nervous and circulatory systems.

10 The tachykinins are distinguished by a conserved carboxyl-terminal
sequence:

Phe-X-Gly-Leu-Met-NH₂

At present, there are three known mammalian tachykinins referred
to as substance P, neurokinin A (NKA, substance K, neuromedin L) and
15 neurokinin B (NKB, neuromedin K) (for review see J.E. Maggio, *Peptides*
(1985) 6(suppl. 3), 237-242). The current nomenclature designates the
three tachykinin receptors mediating the biological actions of substance P,
NKA and NKB as the NK₁, NK₂ and NK₃ receptors, respectively.

Evidence for the usefulness of tachykinin receptor antagonists in
20 pain, headache, especially migraine, Alzheimer's disease, multiple
sclerosis, attenuation of morphine withdrawal, cardiovascular changes,
oedema, such as oedema caused by thermal injury, chronic inflammatory
diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity
and other respiratory diseases including allergic rhinitis, inflammatory
25 diseases of the gut including ulcerative colitis and Crohn's disease, ocular
injury and ocular inflammatory diseases, proliferative vitreoretinopathy,
irritable bowel syndrome and disorders of bladder function including
cystitis and bladder detrusor hyper-reflexia is reviewed in "Tachykinin
Receptors and Tachykinin Receptor Antagonists", C.A. Maggi, R.
30 Patacchini, P. Rovero and A. Giachetti, *J. Auton. Pharmacol.* (1993) 13,
23-93.

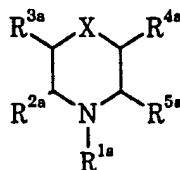
For instance, substance P is believed inter alia to be involved in the neurotransmission of pain sensations [Otsuka *et al*, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in *1982 Substance P in the Nervous System*, Ciba Foundation Symposium 91, 13-34 (published by Pitman) and Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" *TIPS* (1987) 8, 506-510], specifically in the transmission of pain in migraine (B.E.B. Sandberg *et al*, *J. Med Chem.*, (1982) 25, 1009) and in arthritis [Levine *et al Science* (1984) 226, 547-549]. Tachykinins have also been implicated in gastrointestinal (GI) disorders and diseases of the GI tract such as inflammatory bowel disease [Mantyh *et al Neuroscience* (1988) 25(3), 817-37 and D. Regoli in "Trends in Cluster Headache" Ed. Sicuteri *et al* Elsevier Scientific Publishers, Amsterdam (1987) page 85] and emesis [F. D. Tattersall *et al*, *Eur. J. Pharmacol.*, (1993) 250, R5-R6]. It is also hypothesised that there is a neurogenic mechanism for arthritis in which substance P may play a role [Kidd *et al* "A Neurogenic Mechanism for Symmetrical Arthritis" in *The Lancet*, 11 November 1989 and Grönblad *et al*, "Neuropeptides in Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in *J. Rheumatol.* (1988) 15(12), 1807-10]. Therefore, substance P is believed to be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis, and fibrositis [O'Byrne *et al*, *Arthritis and Rheumatism* (1990) 33, 1023-8]. Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions [Hamelet *et al*, *Can. J. Pharmacol. Physiol.* (1988) 66, 1361-7], immunoregulation [Lotz *et al*, *Science* (1988) 241, 1218-21 and Kimball *et al*, *J. Immunol.* (1988) 141(10), 3564-9] vasodilation, bronchospasm, reflex or neuronal control of the viscera [Mantyh *et al*, *PNAS* (1988) 85, 3235-9] and, possibly by arresting or slowing β -amyloid-mediated neurodegenerative changes [Yankner *et al*, *Science* (1990) 250, 279-82] in senile dementia of the Alzheimer type, Alzheimer's disease and Down's Syndrome.

Tachykinin antagonists may also be useful in the treatment of small cell carcinomas, in particular small cell lung cancer (SCLC) [Langdon *et al*, *Cancer Research* (1992) 52, 4554-7].

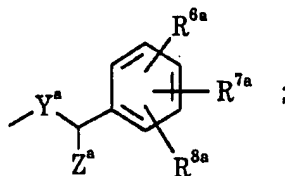
Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis [J. Lubner-Narod *et al*, poster *C.I.N.P. XVIIIth Congress*, 28th June-2nd July 1992], and in disorders of bladder function such as bladder detrusor hyper-reflexia (*Lancet*, 16th May 1992, 1239).

It has furthermore been suggested that tachykinins have utility in the following disorders: depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders related to immune enhancement or suppression such as systemic lupus erythmatosus (European patent specification no. 0 436 334), ophthalmic disease such as conjunctivitis, vernal conjunctivitis, and the like, and cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis (European patent specification no. 0 394 989).

European patent specification no. 0 577 394 (published 5th January 1994) discloses morpholine and thiomorpholine tachykinin receptor antagonists of the general formula



wherein R^{1a} is a large variety of substituents;
 R^{2a} and R^{3a} are *inter alia* hydrogen;
 R^{4a} is *inter alia*



R^{5a} is *inter alia* optionally substituted phenyl;

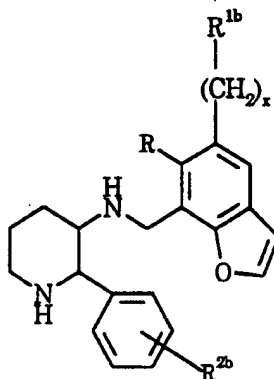
R^{6a} , R^{7a} and R^{8a} are a variety of substituents;

X^a is O, S, SO or SO_2 ;

5 Y^a is *inter alia* O; and

Z^a is hydrogen or C_{1-4} alkyl.

International Patent Specification no. WO 95/06645 discloses piperidine derivatives as tachykinin receptor antagonists of the general formula



10

wherein R is hydrogen or C_{1-4} alkoxy;

R^{1b} is phenyl, optionally substituted by $-(CH_2)_{1-2}CONR^{3b}R^{4b}$ or $S(O)_1$.

R^{2b} , or a 5- or 6-membered aromatic heterocycle containing 1, 2, 3 or 4

15 heteroatoms selected from O, N, or S, optionally substituted by C_{1-4} alkyl,

CF_3 , CN or $-(CH_2)_{1-2}CONR^{3b}R^{4b}$;

R^{2b} is hydrogen or halogen;

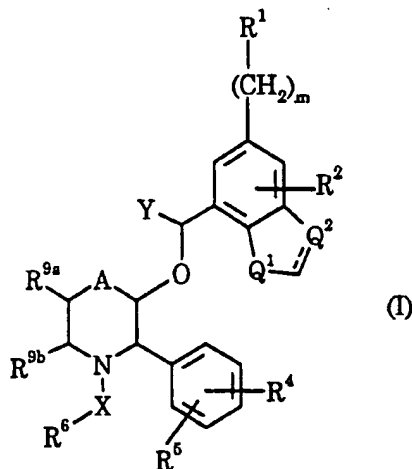
R^{3b} and R^{4b} are hydrogen or C_{1-4} alkyl; and

x is zero or 1.

20

We have now found a further class of non-peptides which are potent antagonists of tachykinins, especially of substance P.

The present invention provides compounds of the formula (I):



wherein

- R^1 is phenyl or a 5- or 6-membered aromatic heterocyclic group containing 1, 2, 3 or 4 heteroatoms, selected from nitrogen, oxygen and sulphur, which aryl or heteroaryl group is optionally substituted by one or two substituents selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, CF_3 , OCF_3 , NO_2 , CN , SR^a , SOR^a , SO_2R^a , COR^a , CO_2R^a , $(CH_2)_nCONR^aR^b$, $(CH_2)_nNR^aR^b$ or $(CH_2)_nNR^aCOR^b$, where R^a and R^b are independently hydrogen or C_{1-4} alkyl and n is zero, 1 or 2;

R^2 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, CF_3 , OCF_3 , NO_2 , CN , SR^a , SOR^a , SO_2R^a , CO_2R^a , $CONR^aR^b$, C_{2-6} alkenyl, C_{2-6} alkynyl or C_{1-4} alkyl substituted by C_{1-4} alkoxy, where R^a and R^b each independently represent hydrogen or C_{1-4} alkyl;

- R^4 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, CF_3 , NO_2 , CN , SR^a , SOR^a , SO_2R^a , CO_2R^a , $CONR^aR^b$, C_{2-6} alkenyl, C_{2-6} alkynyl or C_{1-4} alkyl substituted by C_{1-4} alkoxy, where R^a and R^b each independently represent hydrogen or C_{1-4} alkyl;

- R^5 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy substituted by C_{1-4} alkoxy or CF_3 ;

R^6 is a 5-membered or 6-membered heterocyclic ring containing 2 or 3 nitrogen atoms optionally substituted by $=O$, $=S$ or a C_{1-4} alkyl group, and optionally substituted by a group of the formula ZNR^7R^8 where

Z is C₁₋₆alkylene or C₃₋₆cycloalkylene;

R⁷ is hydrogen, C₁₋₄alkyl, C₃₋₇cycloalkyl or C₃₋₇cycloalkylC₁₋₄alkyl, or C₂₋₄alkyl substituted by C₁₋₄alkoxy or hydroxyl;

R⁸ is hydrogen, C₁₋₄alkyl, C₃₋₇cycloalkyl or C₃₋₇cycloalkylC₁₋₄alkyl, or
5 C₂₋₄alkyl substituted by one or two substituents selected from C₁₋₄alkoxy, hydroxyl or a 4, 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S;

or R⁷, R⁸ and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by one or
10 two groups selected from hydroxy or C₁₋₄alkyl optionally substituted by a C₁₋₄alkoxy or hydroxyl group, and optionally containing a double bond, which ring may optionally contain an oxygen or sulphur ring atom, a group S(O) or S(O)₂ or a second nitrogen atom which will be part of a NH or NR^c moiety where R^c is C₁₋₄alkyl optionally substituted by hydroxy or
15 C₁₋₄alkoxy;

or R⁷, R⁸ and the nitrogen atom to which they are attached form a non-aromatic azabicyclic ring system of 6 to 12 ring atoms;

or Z, R⁷ and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms which may optionally contain an
20 oxygen ring atom;

R^{9a} and R^{9b} are each independently hydrogen or C₁₋₄alkyl, or R^{9a} and R^{9b} are joined so, together with the carbon atoms to which they are attached, there is formed a C₃₋₇ ring;

the dotted line is an optional double bond;

25 A is -O- or -CH₂-;

Q¹ is oxygen, sulphur or -NH-;

Q² is -N=, -NH-, -CH= or -CH₂-;

X is an alkylene chain of 1 to 4 carbon atoms optionally substituted by oxo;

30 Y is hydrogen or a C₁₋₄alkyl group optionally substituted by a hydroxyl group; and

m is zero or 1;

and pharmaceutically acceptable salts and prodrugs thereof.

According to an alternative aspect of the present invention, Y is a C₁₋₄alkyl group optionally substituted by a hydroxyl group.

5 Certain particularly apt compounds of the present invention include those wherein R¹ is a group selected from phenyl, pyrrole, furan, thiene, pyridine, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, pyrazine, pyrimidine, pyridazine, triazole, oxadiazole, thiadiazole, triazine, and tetrazole, each of which aryl or heteroaryl groups being
10 optionally substituted as previously defined.

Preferred compounds of the present invention are those wherein R¹ is a group selected from phenyl, furan, pyridine, pyrazole, imidazole, oxazole, isoxazole, pyrazine, pyrimidine, thiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole and tetrazole, each of which
15 aryl or heteroaryl groups being optionally substituted as previously defined.

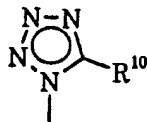
Particularly preferred compounds of the present invention are those wherein R¹ is a group selected from phenyl, furan, pyridine, pyrimidine, 1,2,3-triazole, 1,2,4-triazole and tetrazole.

20 An especially preferred class of compound of formula (I) is that wherein R¹ is the group



25 where R¹⁰ is halogen, C₁₋₆alkyl, C₁₋₆alkoxy, CF₃, OCF₃, NO₂, CN, SR^a, SOR^a, SO₂R^a, COR^a, CO₂R^a, (CH₂)_nCONR^aR^b, (CH₂)_nNR^aR^b or (CH₂)_nNR^aCOR^b, where R^a and R^b are hydrogen or C₁₋₄alkyl, and n is zero, 1 or 2.

Another especially preferred class of compound of formula (I) is that wherein R¹ is the group



5

wherein R¹⁰ is as previously defined.

R¹⁰ is preferably hydrogen, C₁₋₄alkyl, especially methyl, CF₃, (CH₂)_nCONR^aR^b, SOR^a or SO₂R^a where R^a, R^b and n are as previously defined.

10

Most aptly R² is hydrogen, C₁₋₄alkyl, C₁₋₄alkoxy, halogen, CF₃ or OCF₃.

Preferably R² is hydrogen or methoxy, especially hydrogen.

The group R² may be attached to any available position on the 6/5-fused ring. Most preferably R² is attached to the carbon atom inbetween the group R¹-(CH₂)_m- and the remainder of the molecule.

15

Most aptly R⁴ is hydrogen.

Most aptly R⁵ is hydrogen, fluorine, chlorine or CF₃.

Preferably R⁴ is hydrogen and R⁵ is hydrogen or 4-fluoro.

Most aptly R^{9a} and R^{9b} are each independently hydrogen or methyl.

20

Preferably R^{9a} is hydrogen. Preferably R^{9b} is hydrogen. Most preferably R^{9a} and R^{9b} are both hydrogen.

Preferably m is zero.

Preferably A is -O-.

Preferably Q¹ is an oxygen atom.

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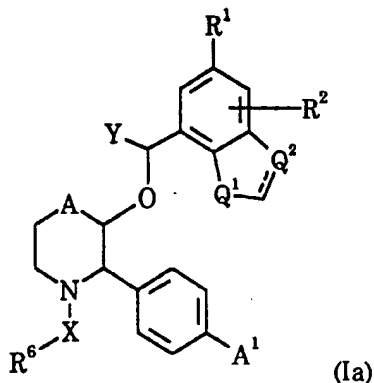
Preferably Q² is -CH= or -CH₂-.

Preferably the dotted line represents a double bond.

Regarding the definition of R¹ above, where R¹ represents 5- or 6-membered aromatic heterocyclic group, such a group may be attached to the remainder of the molecule via any available carbon or nitrogen atom.

5 When R¹ is an aromatic heterocyclic group, preferred substituents include methyl, CN, CF₃ or CON(CH₃)₂. For instance, when R¹ is a pyridine group, suitable substituents include methyl, CN and CON(CH₃)₂; when R¹ is a pyrazole, imidazole, isoxazole or triazole group, suitable substituents include one or two methyl groups; and when R¹ is tetrazole, 10 suitable substituents include methyl or CF₃.

From the foregoing it will be appreciated that a particularly apt sub-group of compounds of this invention are those of the formula (Ia) and pharmaceutically acceptable salts and prodrugs thereof:



A, X, Y, R¹, R², R⁶, Q¹, Q² and the dotted line are as defined in relation to formula (I) and A¹ is fluorine or hydrogen.

According to a second or further aspect of the present invention, a preferred class of compound of formula (I) or (Ia) is that wherein Y represents a C₁₋₄alkyl group; or a pharmaceutically acceptable salt or prodrug thereof.

According to a further or alternative aspect of the present invention, another preferred class of compound of formula (I) or (Ia) is that wherein

R^6 is substituted at least by a group of the formula ZNR^7R^8 as defined above; or a pharmaceutically acceptable salt or prodrug thereof.

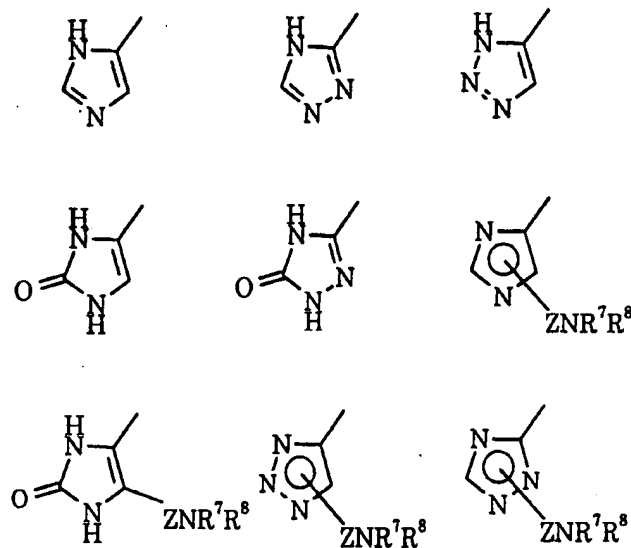
When the group Y in compounds of the formulae (I) or (Ia) is a C_{1-4} alkyl group substituted by a hydroxy group, a preferred group is the
 5 CH_2OH group.

Another preferred group Y for compounds of the formulae (I) or (Ia) is the CH_3 group.

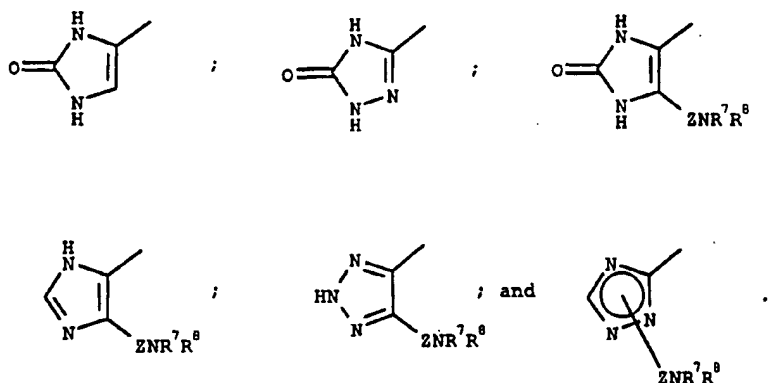
Particularly apt values for X for compounds of the formulae (I) or (Ia) include CH_2 , $CH(CH_3)$ and CH_2CH_2 of which the CH_2 group is
 10 preferred.

Favourably R^6 is a 5-membered ring.

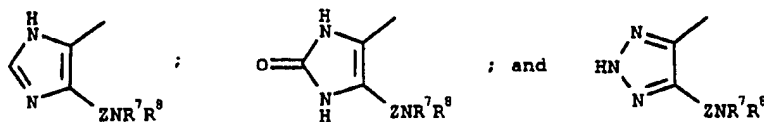
In particular, R^6 may, represent a heterocyclic ring selected from:



Particularly preferred heterocyclic rings represented by R^6 are
 15 selected from:

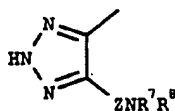


Most especially, R^6 may represent a heterocyclic ring selected from:

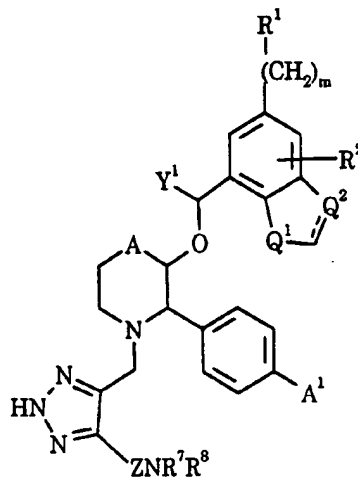


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A particularly preferred heterocyclic ring represented by R^6 is:



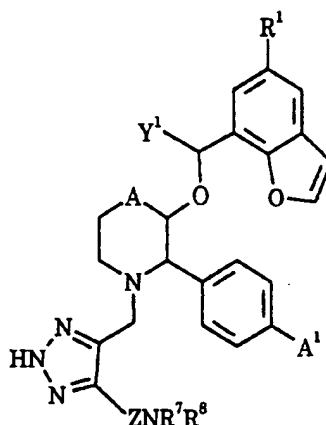
One favoured group of compounds of this invention are of the formula (Ib) and pharmaceutically acceptable salts thereof:



(Ib)

wherein A^1 is as defined in relation to formula (Ia), wherein A, Z, R^1 , R^2 , R^7 , R^8 , Q^1 , Q^2 , the dotted line and m are as defined in relation to formula (I) and wherein Y^1 is hydrogen or methyl.

A further favoured group of compounds of the present invention are
 5 of the formula (Ic) and pharmaceutically acceptable salts thereof:



(Ic)

wherein A^1 is as defined in relation to formula (Ia); Y^1 is hydrogen or
 10 methyl; and R^1 , R^7 , R^8 and Z are as defined in relation to formula (I).

With respect to compounds of the formulae (I), (Ia), (Ib), and (Ic), Z may be a linear, branched or cyclic group. Favourably Z contains 1 to 4 carbon atoms and most favourably 1 or 2 carbon atoms. A particularly favourable group Z is CH_2 .

15 With respect to compounds of the formulae (I), (Ia), (Ib), and (Ic), R^7 may aptly be a C_{1-4} alkyl group or a C_{2-4} alkyl group substituted by a hydroxyl or C_{1-2} alkoxy group, R^8 may aptly be a C_{1-4} alkyl group or a C_{1-4} alkyl group substituted by a hydroxyl or C_{1-2} alkoxy group, or R^7 and R^8 may be linked so that, together with the nitrogen atom to which they are
 20 attached, they form an azetidiny, pyrrolidinyl, piperidyl, morpholino, thiomorpholino, piperazino or piperazino group substituted on the

nitrogen atom by a C₁₋₄alkyl group or a C₂₋₄alkyl group substituted by a hydroxy or C₁₋₂alkoxy group.

Where the group NR⁷R⁸ represents a heteroaliphatic ring of 4 to 7 ring atoms and said ring contains a double bond, a particularly preferred group is 3-pyrroline.

Where the group NR⁷R⁸ represents a non-aromatic azabicyclic ring system, such a system may contain between 6 and 12, and preferably between 7 and 10, ring atoms. Suitable rings include 5-azabicyclo[2.1.1]hexyl, 5-azabicyclo[2.2.1]heptyl, 6-azabicyclo[3.2.1]octyl, 2-azabicyclo[2.2.2]octyl, 6-azabicyclo[3.2.2]nonyl, 6-azabicyclo[3.3.1]nonyl, 6-azabicyclo[3.2.2]decyl, 7-azabicyclo[4.3.1]decyl, 7-azabicyclo[4.4.1]undecyl and 8-azabicyclo[5.4.1]dodecyl, especially 5-azabicyclo[2.2.1]heptyl and 6-azabicyclo[3.2.1]octyl.

Where R⁸ represents a C₂₋₄alkyl group substituted by a 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S, suitable rings include pyrrolidino, piperidino, piperazino, morpholino, or thiomorpholino. Particularly preferred are nitrogen containing heteroaliphatic rings, especially pyrrolidino and morpholino rings.

Particularly suitable moieties ZNR⁷R⁸ include those wherein Z is CH₂ or CH₂CH₂ and NR⁷R⁸ is amino, methylamino, dimethylamino, diethylamino, azetidiny, pyrrolidino and morpholino.

Further preferred moieties represented by ZNR⁷R⁸ are those wherein Z is CH₂ or CH₂CH₂, R⁷ represents hydrogen, C₁₋₄alkyl or C₃₋₆cycloalkyl and R⁸ is C₂₋₄alkyl substituted by one or two substituents selected from hydroxy, C₁₋₂alkoxy, azetidiny, pyrrolidino, piperidino, morpholino or thiomorpholino.

In particular, Z is preferably CH₂ and NR⁷R⁸ is preferably dimethylamino, azetidiny or pyrrolidino, especially dimethylamino.

As used herein, the term "alkyl" or "alkoxy" as a group or part of a group means that the group is straight or branched. Examples of suitable

alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy.

The cycloalkyl groups referred to herein may represent, for
5 example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. A suitable cycloalkylalkyl group may be, for example, cyclopropylmethyl.

As used herein, the terms "alkenyl" and "alkynyl" as a group or part
of a group means that the group is straight or branched. Examples of
suitable alkenyl groups include vinyl and allyl. A suitable alkynyl group
10 is propargyl.

When used herein the term halogen means fluorine, chlorine,
bromine and iodine. The most apt halogens are fluorine and chlorine of
which fluorine is preferred.

Specific compounds within the scope of this invention include:
15 [2S,3S]-1-[(5-(dimethylaminomethyl)-1H-[1,2,3]triazol-4-yl)methyl]-2-
phenyl-3-[[5-(1-methyl-1H-1,2,3-triazol-5-yl)benzofuran-7-yl]methoxy]
piperidine;
[2S,3S]-1-[(5-(dimethylaminomethyl)-1H-[1,2,3]triazol-4-yl)methyl]-2-
phenyl-3-[[5-(5-methyl-1H-tetrazol-1-yl)benzofuran-7-yl]methoxy]
20 piperidine;
and pharmaceutically acceptable salts or prodrugs thereof.

Further preferred compounds within the scope of the present
invention are described in the Examples described herein.

In a further aspect of the present invention, the compounds of
25 formula (I) will preferably be prepared in the form of a pharmaceutically
acceptable salt, especially an acid addition salt.

For use in medicine, the salts of the compounds of formula (I) will
be non-toxic pharmaceutically acceptable salts. Other salts may, however,
be useful in the preparation of the compounds according to the invention
30 or of their non-toxic pharmaceutically acceptable salts. Suitable
pharmaceutically acceptable salts of the compounds of this invention

include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or sulphuric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible *in vivo* into the required compound of formula (I).

Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

A prodrug may be a pharmacologically inactive derivative of a biologically active substance (the "parent drug" or "parent molecule") that requires transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. The transformation *in vivo* may be, for example, as the result of some metabolic process, such as chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulphate ester, or reduction or oxidation of a susceptible functionality.

Thus, for example, certain preferred prodrugs may not be antagonists of tachykinin, particularly substance P, activity to any significant extent (or not at all). Such compounds, however, are still

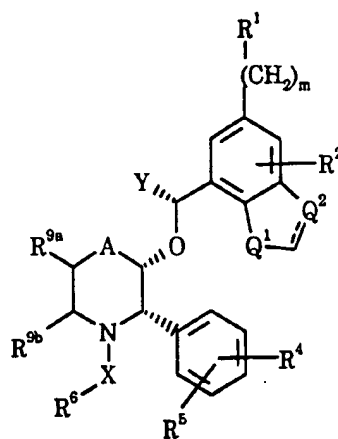
advantageous in treating the various conditions described herein, especially where an injectable formulation is preferred.

The advantages of a prodrug may lie in its physical properties, such as enhanced water solubility for parenteral administration compared with the parent drug, or it may enhance absorption from the digestive tract, or it may enhance drug stability for long-term storage. Ideally a prodrug will improve the overall efficacy of a parent drug, for example, through the reduction of toxicity and unwanted effects of drugs by controlling their absorption, blood levels, metabolism, distribution and cellular uptake.

The present invention includes within its scope solvates of the compounds of formula (I) and salts thereof, for example, hydrates.

The compounds according to the invention have at least three asymmetric centres, and may accordingly exist both as enantiomers and as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The preferred compounds of the formula (I), (Ia), (Ib) and (Ic), will have the 2- and 3- substituent cis. The preferred stereochemistry at the 2-position is either (R) when A is -O- or (S) when A is -CH₂-, for instance, that possessed by the compound of Example 1 (i.e. 2-(S)). The preferred stereochemistry of the 3-position is that possessed by the compound of Example 1 (i.e. 3-(S)). The preferred stereochemistry of the carbon to which the group Y is either (R) when Y is C₁₋₄alkyl (e.g. methyl) or (S) when Y is C₁₋₄alkyl substituted by hydroxy (e.g. CH₂OH). Thus for example as shown in formula (Id)



(Id)

The present invention further provides pharmaceutical compositions comprising one or more compounds of formula (I) in association with a pharmaceutically acceptable carrier.

- 5 Preferably the compositions according to the invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or administration by inhalation or insufflation.

- For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional
 10 tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the
 15 present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.
 20 This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the

novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former.

- 5 The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids
10 with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed
15 oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

- 20 Preferred compositions for administration by injection include those comprising a compound of formula (I), as the active ingredient, in association with a surface-active agent (or wetting agent or surfactant) or in the form of an emulsion (as a water-in-oil or oil-in-water emulsion).

Suitable surface-active agents include anionic agents such as
25 sodium bis-(2-ethylhexyl)sulfosuccinate (docusate sodium), cationic agents, such as alkyltrimethylammonium bromides, (e.g. cetyltrimethylammonium bromide (cetrimide)), and in particular, non-ionic agents, such as polyoxyethylenesorbitans (e.g. Tween™ 20, 40, 60, 80 or 85) and other sorbitans (e.g. Span™ 20, 40, 60, 80 or 85). Compositions
30 with a surface-active agent will conveniently comprise between 0.05 and 5% surface-active agent, and preferably between 0.1 and 2.5%. It will be

appreciated that other ingredients may be added, for example mannitol or other pharmaceutically acceptable vehicles, if necessary.

Suitable emulsions may be prepared using commercially available fat emulsions, such as Intralipid™, Liposyn™, Infontrol™, Lipofundin™ and Lipiphysan™. The active ingredient may be either dissolved in a pre-mixed emulsion composition or alternatively it may be dissolved in an oil (e.g. soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an emulsion formed upon mixing with a phospholipid (e.g. egg phospholipids, soybean phospholipids or soybean lecithin) and water.

It will be appreciated that other ingredients may be added, for example glycerol or glucose, to adjust the tonicity of the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. The fat emulsion will preferably comprise fat droplets between 0.1 and 1.0µm, particularly 0.1 and 0.5µm, and have a pH in the range of 5.5 to 8.0.

Particularly preferred emulsion compositions are those prepared by mixing a compound of formula (I) with Intralipid™ or the components thereof (soybean oil, egg phospholipids, glycerol and water).

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The present invention further provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), which process comprises bringing a compound of formula (I) into association with a pharmaceutically acceptable carrier or excipient.

5 The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity.

Thus, for example, an excess of tachykinin, and in particular substance P, activity is implicated in a variety of disorders of the central nervous system. Such disorders include mood disorders, such as depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder; anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalised anxiety disorders; schizophrenia and other psychotic disorders, for example, schizophreniform disorders, schizoaffective disorders, delusional disorders, brief psychotic disorders, shared psychotic disorders and psychotic disorders with delusions or hallucinations; delirium, dementia, and amnestic and other cognitive or neurodegenerative disorders, such as Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, vascular dementia, and other dementias, for example, due to HIV disease, head trauma, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, or due to multiple aetiologies; Parkinson's disease and other extra-pyramidal movement disorders such as medication-induced movement disorders, for example, neuroleptic-induced parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive

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dyskinesia and medication-induced postural tremour; substance-related disorders arising from the use of alcohol, amphetamines (or amphetamine-like substances) caffeine, cannabis, cocaine, hallucinogens, inhalants and aerosol propellants, nicotine, opioids, phenylglycidine derivatives, 5 sedatives, hypnotics, and anxiolytics, which substance-related disorders include dependence and abuse, intoxication, withdrawal, intoxication delirium, withdrawal delirium, persisting dementia, psychotic disorders, mood disorders, anxiety disorders, sexual dysfunction and sleep disorders; epilepsy; Down's syndrome; demyelinating diseases such as MS and ALS 10 and other neuropathological disorders such as peripheral neuropathy, for example diabetic and chemotherapy-induced neuropathy, and postherpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia and other neuralgias; and cerebral vascular disorders due to acute or chronic cerebrovascular damage such as cerebral infarction, subarachnoid 15 haemorrhage or cerebral oedema.

Tachykinin, and in particular substance P, activity is also involved in nociception and pain. The compounds of the present invention will therefore be of use in the prevention or treatment of diseases and conditions in which pain predominates, including soft tissue and 20 peripheral damage, such as acute trauma, osteoarthritis, rheumatoid arthritis, musculo-skeletal pain, particularly after trauma, spinal pain, myofascial pain syndromes, headache, episiotomy pain, and burns; deep and visceral pain, such as heart pain, muscle pain, eye pain, orofacial pain, for example, odontalgia, abdominal pain, gynaecological pain, for 25 example, dysmenorrhoea, and labour pain; pain associated with nerve and root damage, such as pain associated with peripheral nerve disorders, for example, nerve entrapment and brachial plexus avulsions, amputation, peripheral neuropathies, tic douloureux, atypical facial pain, nerve root damage, and arachnoiditis; pain associated with carcinoma, often referred 30 to as cancer pain; central nervous system pain, such as pain due to spinal

cord or brain stem damage; low back pain; sciatica; ankylosing spondylitis, gout; and scar pain.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of respiratory diseases, particularly those
5 associated with excess mucus secretion, such as chronic obstructive
airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and
asthma, adult respiratory distress syndrome, and bronchospasm;
inflammatory diseases such as inflammatory bowel disease, psoriasis,
fibrositis, osteoarthritis, rheumatoid arthritis, pruritis and sunburn;
10 allergies such as eczema and rhinitis; hypersensitivity disorders such as
poison ivy; ophthalmic diseases such as conjunctivitis, vernal
conjunctivitis, and the like; ophthalmic conditions associated with cell
proliferation such as proliferative vitreoretinopathy; cutaneous diseases
such as contact dermatitis, atopic dermatitis, urticaria, and other
15 eczematoid dermatitis.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of neoplasms, including breast tumours, neuroganglioblastomas and small cell carcinomas such as small cell lung cancer.

20 Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of gastrointestinal (GI) disorders, including inflammatory disorders and diseases of the GI tract such as gastritis, gastroduodenal ulcers, gastric carcinomas, gastric lymphomas, disorders associated with the neuronal control of viscera, ulcerative colitis, Crohn's
25 disease, irritable bowel syndrome and emesis, including acute, delayed or anticipatory emesis such as emesis induced by chemotherapy, radiation, toxins, viral or bacterial infections, pregnancy, vestibular disorders, for example, motion sickness, vertigo, dizziness and Meniere's disease, surgery, migraine, variations in intracranial pressure, gastro-oesophageal
30 reflux disease, acid indigestion, over indulgence in food or drink, acid

stomach, waterbrash or regurgitation, heartburn, for example, episodic, nocturnal or meal-induced heartburn, and dyspepsia.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of a variety of other conditions including stress
5 related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; plasma extravasation resulting from cytokine chemotherapy, disorders of
10 bladder function such as cystitis, bladder detrusor hyper-reflexia and incontinence; fibrosing and collagen diseases such as scleroderma and eosinophilic fasciitis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, vascular headache, migraine and Reynaud's disease; and pain or nociception attributable to or associated
15 with any of the foregoing conditions, especially the transmission of pain in migraine.

The compounds of formula (I) are also of value in the treatment of a combination of the above conditions, in particular in the treatment of combined post-operative pain and post-operative nausea and vomiting.

20 The compounds of formula (I) are particularly useful in the treatment of emesis, including acute, delayed or anticipatory emesis, such as emesis induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, motion, surgery, migraine, and variations in intracranial pressure. Most especially, the compounds of formula (I) are
25 of use in the treatment of emesis induced by antineoplastic (cytotoxic) agents including those routinely used in cancer chemotherapy.

Examples of such chemotherapeutic agents include alkylating agents, for example, nitrogen mustards, ethyleneimine compounds, alkyl sulphonates and other compounds with an alkylating action such as
30 nitrosoureas, cisplatin and dacarbazine; antimetabolites, for example, folic acid, purine or pyrimidine antagonists; mitotic inhibitors, for example,

vinca alkaloids and derivatives of podophyllotoxin; and cytotoxic antibiotics.

Particular examples of chemotherapeutic agents are described, for instance, by D. J. Stewart in *Nausea and Vomiting: Recent Research and Clinical Advances*, Eds. J. Kucharczyk *et al*, CRC Press Inc., Boca Raton, Florida, USA (1991) pages 177-203, especially page 188. Commonly used chemotherapeutic agents include cisplatin, dacarbazine (DTIC), dactinomycin, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, carmustine (BCNU), lomustine (CCNU), doxorubicin (adriamycin), daunorubicin, procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5-fluorouracil, vinblastine, vincristine, bleomycin and chlorambucil [R. J. Gralla *et al* in *Cancer Treatment Reports* (1984) 68(1), 163-172].

The compounds of formula (I) are also of use in the treatment of emesis induced by radiation including radiation therapy such as in the treatment of cancer, or radiation sickness; and in the treatment of post-operative nausea and vomiting.

It will be appreciated that the compounds of formula (I) may be presented together with another therapeutic agent as a combined preparation for simultaneous, separate or sequential use for the relief of emesis. Such combined preparations may be, for example, in the form of a twin pack.

A further aspect of the present invention comprises the compounds of formula (I) in combination with a 5-HT₃ antagonist, such as ondansetron, granisetron or tropisetron, or other anti-emetic medicaments, for example, a dopamine antagonist such as metoclopramide. Additionally, a compound of formula (I) may be administered in combination with an anti-inflammatory corticosteroid, such as dexamethasone. Furthermore, a compound of formula (I) may be administered in combination with a chemotherapeutic agent such as an alkylating agent, antimetabolite, mitotic inhibitor or cytotoxic antibiotic,

as described above. In general, the currently available dosage forms of the known therapeutic agents for use in such combinations will be suitable.

When tested in the ferret model of cisplatin-induced emesis described by F. D. Tattersall *et al*, in *Eur. J. pharmacol.*, (1993) 250, R5-
5 R6, the compounds of the present invention were found to attenuate the retching and vomiting induced by cisplatin.

The compounds of formula (I) are also particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic
10 and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteoarthritis, rheumatoid arthritis and headache, including migraine, acute or chronic tension headache, cluster headache, temporomandibular pain, and maxillary sinus pain.

The present invention further provides a compound of formula (I)
15 for use in therapy.

According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P.

20 The present invention also provides a method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I) or a composition comprising a
25 compound of formula (I).

For the treatment of certain conditions it may be desirable to employ a compound according to the present invention in conjunction with another pharmacologically active agent. For example, for the treatment of respiratory diseases such as asthma, a compound of formula (I) may be
30 used in conjunction with a bronchodilator, such as a β_2 -adrenergic receptor agonist or tachykinin antagonist which acts at NK-2 receptors.

The compound of formula (I) and the bronchodilator may be administered to a patient simultaneously, sequentially or in combination.

Likewise, a compound of the present invention may be employed with a leukotriene antagonists, such as a leukotriene D₄ antagonist such
5 as a compound selected from those disclosed in European patent specification nos. 0 480 717 and 0 604 114 and in US patent nos. 4,859,692 and 5,270,324. This combination is particularly useful in the treatment of respiratory diseases such as asthma, chronic bronchitis and cough.

The present invention accordingly provides a method for the
10 treatment of a respiratory disease, such as asthma, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula (I) and an effective amount of a bronchodilator.

The present invention also provides a composition comprising a
15 compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

It will be appreciated that for the treatment or prevention of migraine, a compound of the present invention may be used in conjunction with other anti-migraine agents, such as ergotamines or 5-HT₁ agonists,
20 especially sumatriptan.

Likewise, for the treatment of behavioural hyperalgesia, a compound of the present invention may be used in conjunction with an antagonist of N-methyl D-aspartate (NMDA), such as dizocilpine.

For the treatment or prevention of inflammatory conditions in the
25 lower urinary tract, especially cystitis, a compound of the present invention may be used in conjunction with an anti-inflammatory agent such as a bradykinin receptor antagonist.

The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically
30 acceptable carrier.

It will be appreciated that for the treatment or prevention of pain or nociception, a compound of the present invention may be used in conjunction with other analgesics, such as acetaminophen (paracetamol), aspirin and other NSAIDs and, in particular, opioid analgesics, especially morphine. Specific anti-inflammatory agents include diclofenac, ibuprofen, indomethacin, ketoprofen, naproxen, piroxicam and sulindac. Suitable opioid analgesics of use in conjunction with a compound of the present invention include morphine, codeine, dihydrocodeine, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxymorphone, alfentanil, buprenorphine, butorphanol, fentanyl, sufentanyl, meperidine, methadone, nalbuphine, propoxyphene and pentazocine; or a pharmaceutically acceptable salt thereof. Preferred salts of these opioid analgesics include morphine sulphate, morphine hydrochloride, morphine tartrate, codeine phosphate, codeine sulphate, dihydrocodeine bitartrate, diacetylmorphine hydrochloride, hydrocodone bitartrate, hydromorphone hydrochloride, levorphanol tartrate, oxymorphone hydrochloride, alfentanil hydrochloride, buprenorphine hydrochloride, butorphanol tartrate, fentanyl citrate, meperidine hydrochloride, methadone hydrochloride, nalbuphine hydrochloride, propoxyphene hydrochloride, propoxyphene napsylate (2-naphthalenesulphonic acid (1:1) monohydrate), and pentazocine hydrochloride.

Therefore, in a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of the present invention and an analgesic, together with at least one pharmaceutically acceptable carrier or excipient.

In a further or alternative aspect of the present invention, there is provided a product comprising a compound of the present invention and an analgesic as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of pain or nociception.

The excellent pharmacological profile of the compounds of the present invention offers the opportunity for their use in therapy at low doses thereby minimising the risk of unwanted side effects.

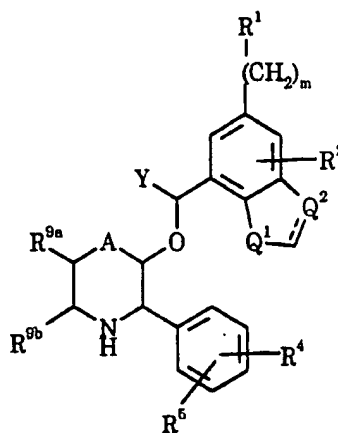
In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day.

For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

In the treatment of emesis using an injectable formulation, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially 0.01 to 1 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

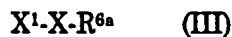
It will be appreciated that the amount of a compound of formula (I) required for use in any treatment will vary not only with the particular compounds or composition selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician.

According to a general process (A), the compounds according to the invention may be prepared from compounds of formula (II)



(II)

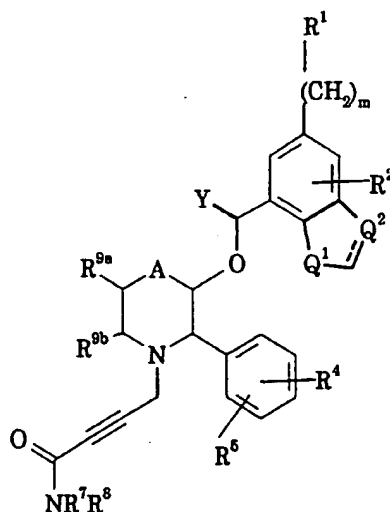
wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^{9a} , R^{9b} , A, Y, Q^1 , Q^2 , the dotted line and m are
 as defined in relation to formula (I) by reaction with a compound of
 5 formula (III):



where X is as defined in relation to formula (I), R^{6a} is a group of the
 10 formula R^6 as defined in relation to formula (I) or a precursor therefor and
 X^1 is a leaving group such as bromine or chlorine; and, if R^{6a} is a precursor
 group, converting it to a group R^6 (in which process any reactive group
 may be protected and thereafter deprotected if desired).

This reaction may be performed in conventional manner, for
 15 example in an organic solvent such as dimethylformamide in the presence
 of an acid acceptor such as potassium carbonate.

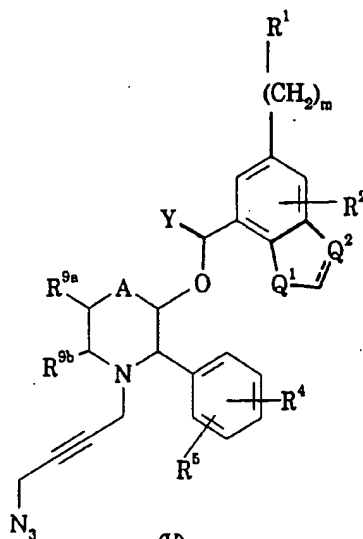
According to another process (B), compounds of formula (I) wherein
 R^6 represents 1,2,3-triazol-4-yl substituted by $CH_2NR^7R^8$, and X is $-CH_2-$,
 may be prepared by reaction of a compound of formula (IV)



(IV)

with an azide, for example, sodium azide in a suitable solvent such as dimethylsulphoxide at a temperature of between 40°C and 100°C, followed by reduction of the carbonyl group adjacent to $-NR^7R^8$ using a suitable
 5 reducing agent such as lithium aluminium hydride at a temperature between -10°C and room temperature, conveniently at room temperature.

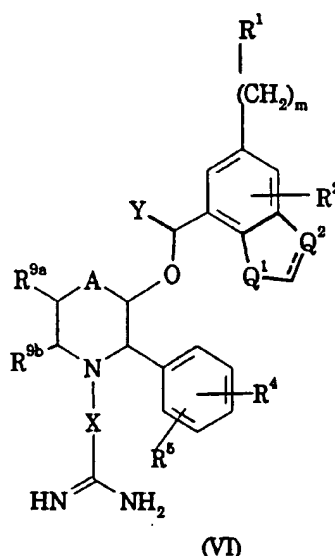
Alternatively, according to a process (C), compounds of formula (I) wherein R^6 represents 1,2,3-triazol-4-yl substituted by $CH_2NR^7R^8$, and X is $-CH_2-$, may be prepared by reaction of a compound of formula (V)



(V)

with an amine of formula NHR^8 , in a suitable solvent such as an ether, for example, dioxan, at elevated temperature, for example, between 50°C and 100°C , in a sealed tube, or the like. This reaction is based upon that described in *Chemische Berichte* (1989) 122, p. 1963.

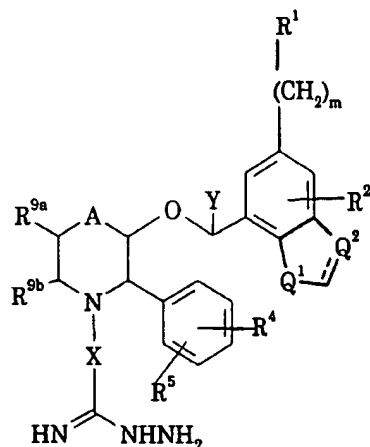
- 5 According to another process, (D), compounds of formula (I) wherein R^6 represents substituted or unsubstituted 1,3,5-triazine may be prepared by reaction of intermediates of formula (VI):



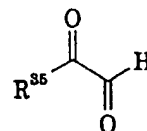
with substituted or unsubstituted 1,3,5-triazine.

- 10 The reaction is conveniently effected in a suitable organic solvent, such as acetonitrile, at elevated temperature, such as $80-90^\circ\text{C}$, preferably about 82°C .

- 15 According to a further process, (E), compounds of formula (I) wherein R^6 represents substituted or unsubstituted 1,2,4-triazine may be prepared by reaction of an intermediate of formula (VII) with a dicarbonyl compound of formula (VIII):



(VII)



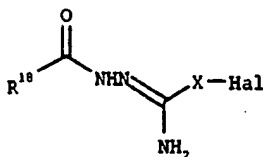
(VIII)

wherein R^{35} represents H or a suitable substituent such as ZNR^7R^8 .

The reaction is conveniently effected in a suitable organic solvent, such as an ether, e.g. tetrahydrofuran, conveniently at ambient temperature.

5

According to a further process (F'), compounds of formula (I) wherein R^6 represents a substituted 1,2,4-triazolyl group may be prepared by reaction of an intermediate of formula (II) with a compound of formula (IX)



(IX)

10

wherein X is as defined in relation to formula (I), Hal is a halogen atom, for example, bromine, chlorine or iodine and R^{18} is H, $CONH_2$ or OCH_3 (which is converted to an oxo substituent under the reaction conditions), in the presence of a base, followed where necessary by conversion to a compound of formula (I), for example, by reduction of the $CONH_2$ group to CH_2NH_2 .

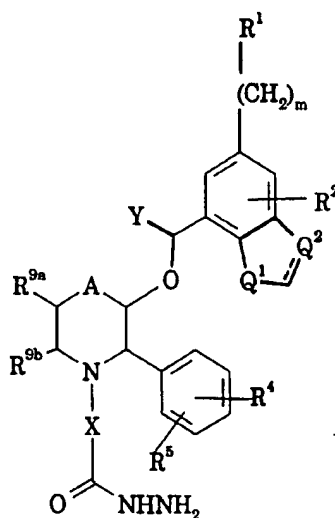
15

Suitable bases of use in the reaction include alkali metal carbonates such as, for example, potassium carbonate. The reaction is conveniently

effected in an anhydrous organic solvent such as, for example, anhydrous dimethylformamide, preferably at elevated temperature, such as about 140°C.

- A suitable reducing agent for the group CONH₂ is lithium
 5 aluminium hydride, used at between -10°C and room temperature.

According to another process, (G), compounds of formula (I) wherein R⁶ represents thioxotriazolyl may be prepared from intermediates of formula (X)

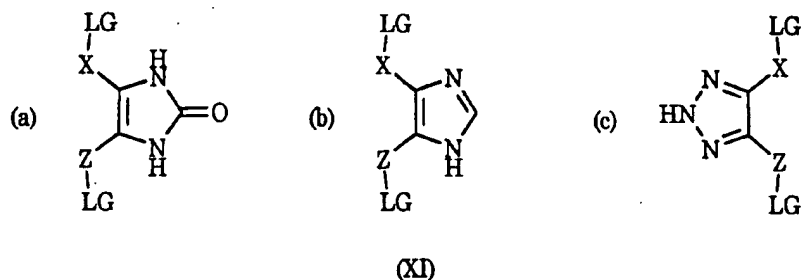


(X)

- 10 by reaction with a compound of formula HNCS, in the presence of a base.

Suitable bases of use in the reaction include organic bases such as, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The reaction is conveniently effected in a suitable organic solvent, such as alcohol, e.g. butanol.

- 15 According to a further alternative general process (H), compounds of formula (I) wherein the heterocycle R⁶ is substituted by ZNR⁷R⁸, may be prepared from an intermediate of formula (II) as defined above with one of the compounds of formula (XI):

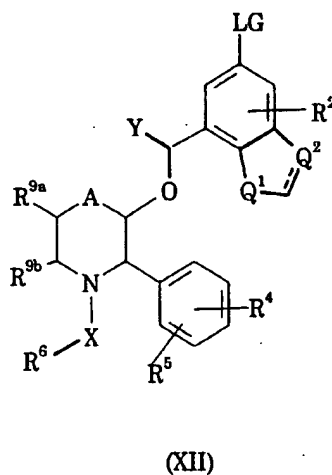


wherein each LG, which may be the same or different, is a leaving group, such as an alkyl- or arylsulphonyloxy group (e.g. mesylate or tosylate) or, in particular, a halogen atom, (e.g. bromine, chlorine or iodine) and X and Z are as defined in formula (I), followed by reaction of the resultant compound with an amine NHR^7R^8 to complete the ZNR^7R^8 moiety.

This reaction is conveniently effected in an organic solvent such as dimethylformamide in the presence of an acid acceptor such as potassium carbonate.

It will be appreciated that, where necessary, reactive groups may be protected, thus for example, the NH groups of an imidazolinone of formula (XIa) may be protected by any suitable amine protecting group such as an acetyl group.

According to another general process (J), compounds of formula (I) may be prepared by reaction of intermediates of formula (XII)



wherein LG is a suitable leaving group such as a halogen atom, e.g. bromine or iodine, or $-\text{OSO}_2\text{CF}_3$, with a compound of formula (XIII)



5

wherein R^{40} is $\text{B}(\text{OH})_2$, $\text{Sn}(\text{alkyl})_3$, for example, $\text{Sn}(\text{methyl})_3$ or $\text{Sn}(\text{n-butyl})_3$. Where R^{40} is $\text{B}(\text{OH})_2$, the reaction is conveniently effected in the presence of a palladium (0) catalyst such as

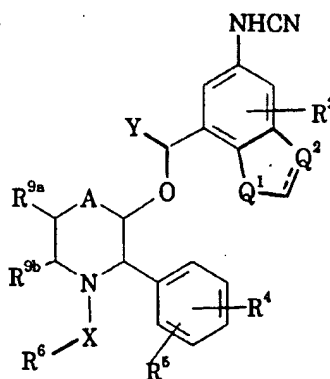
10

tetrakis(triphenylphosphine)palladium (0), in a suitable solvent such as an ether, for example, dimethoxyethane, at an elevated temperature.

Where R^{40} is $\text{Sn}(\text{alkyl})_3$, the reaction is conveniently effected in the presence of a palladium (II) catalyst such as bis(triphenylphosphine) palladium (II) chloride, in a suitable solvent such as an aromatic hydrocarbon, for example, toluene, at an elevated temperature.

15

According to a preferred process (K) compounds of formula (I) wherein R^1 is a tetrazol-1-yl group and m is zero, may be prepared by the reaction of intermediates of formula (XIV)



(XIV)

20

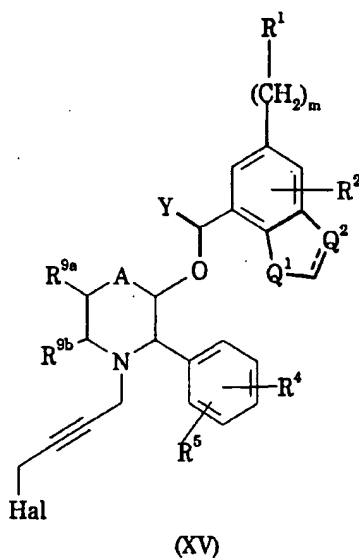
with ammonium chloride and sodium azide at elevated temperature, conveniently in a solvent such as dimethylformamide.

Further details of suitable procedures will be found in the accompanying Examples.

Compounds of formula (I) may also be prepared from other compounds of formula (I) using suitable interconversion procedures. For example, compounds of formula (I) wherein X represents C₁₋₄alkyl may be prepared from compounds of formula (I) wherein X represents C₁₋₄alkyl substituted by oxo by reduction, for example, using borane or lithium aluminium hydride. Suitable interconversion procedures will be readily apparent to those skilled in the art.

Intermediates of formula (IV) may be prepared from intermediates of formula (II) by reaction with an acetylene compound of formula HC≡C-CH₂-Hal in the presence of a base such as potassium carbonate in a suitable solvent such as dimethylformamide, conveniently at room temperature, followed by reaction of the resultant acetylene intermediate with an amide of formula Hal-CO-NR⁷R⁸ in the presence of suitable catalysts including bis(triphenylphosphine) palladium(II) chloride, copper(I) iodide and triphenylphosphine in a suitable solvent such as triethylamine, preferably at reflux.

Intermediates of formula (V) may be prepared from a compound of formula (XV)



wherein Hal is a halogen atom, for example, chlorine, bromine or iodine, especially chlorine, by reaction with an azide, for example, sodium azide in

a suitable solvent such as dimethylsulphoxide at or below room temperature.

Compounds of formula (XV) may be prepared by a dropwise addition of an intermediate of formula (II) to a dihaloacetylene of formula
5 Hal-CH₂-C≡C-CH₂-Hal where each Hal is independently chlorine, bromine or iodine, especially chlorine. The reaction is conveniently effected in a suitable solvent such as dimethylformamide in the presence of a base such as potassium carbonate.

Intermediates of formula (VI) may be prepared from intermediates
10 of formula (II) by reaction with a compound of formula Hal-X-C(NH)NH₂, where Hal and X are as previously defined.

Intermediates of formula (VII) may be prepared from intermediates of formula (II) by reaction with a compound of formula
Hal-X-C(NH)NHNH-Boc, wherein Hal and X are as previously defined
15 and Boc stands for t-butoxycarbonyl, followed by deprotection under acidic conditions.

Compounds of formula (VIII) are commercially available or may be prepared from commercially available compounds by known methods.

Compounds of formula (IX) may be prepared as described in
20 *J. Med. Chem.*, (1984) 27, 849.

Intermediates of formula (X) may be prepared from the corresponding ester by treatment with hydrazine. The reaction is conveniently effected in a suitable organic solvent, such as an alcohol, for example, ethanol, at elevated temperature.

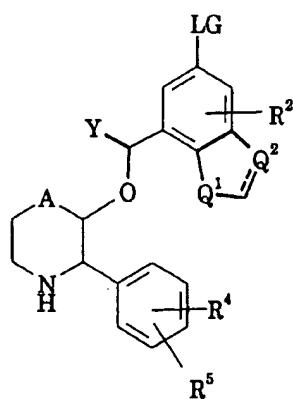
25 For compounds wherein R⁶ is a heterocycle substituted by a ZNR⁷R⁸ group where Z is CH₂, certain favoured compounds of formula (I) may be prepared from a corresponding compound with a hydrogen atom in place of the ZNR⁷R⁸. Thus, for example a compound of the formula (I) wherein R⁶ is an imidazolinone group carrying a CH₂NR⁷R⁸ moiety may be
30 prepared from a corresponding compound lacking the CH₂NR⁷R⁸ moiety by reaction with formaldehyde and an amine NHR⁷R⁸ under conventional

Mannich reaction conditions, for example in methanol with heating. If desired a pre-formed reagent such as $R^7R^8N^+=CH_2.I^-$ may be employed and a tertiary amine such as triethylamine used as acid acceptor.

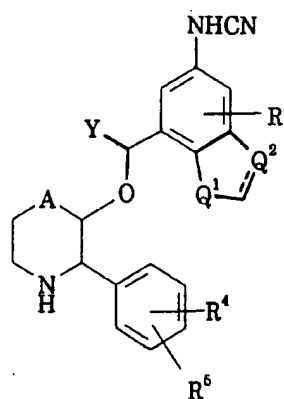
Alternatively a compound of formula (I) wherein R^6 is an
 5 imidazolinone group lacking a $CH_2NR^7R^8$ may be reacted with paraformaldehyde and an amine for example a secondary amine such as pyrrolidine to give a compound wherein the imidazolinone ring is substituted by $CH_2NR^7R^8$ where R^7 , R^8 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms which
 10 may optionally contain an oxygen ring atom or a second nitrogen atom which will be part of a NH or NR^c moiety, where R^c is as previously defined.

This reaction may be performed in a conventional manner, for instance, in a suitable solvent such as an alcohol, for example, methanol
 15 at an elevated temperature up to the boiling point of the solvent.

Compounds of formulae (XII) and (XIV) may be prepared by reacting a compound of formula (XVI) or (XVII)



(XVI)

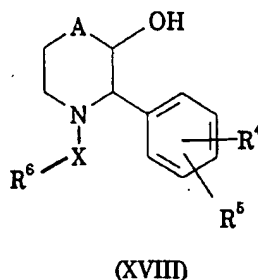


(XVII)

20

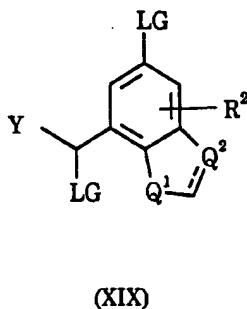
respectively, with any suitable reagent for completing the R^6-X - moiety as described in any one of processes (A) to (H).

Alternatively, compounds of formula (XII) may be prepared by reacting a compound of formula (XVIII)



5

with a compound of formula (XIX)



where each LG independently represents a leaving group as previously defined.

10

Compounds of formula (XIII) and (XIX) may be prepared by conventional methodology, such as that described in International patent specification No. WO 95/06645, published 9th March 1995.

The preferred phosphate prodrugs of the compounds of the present invention are those wherein Y is a derivatized hydroxy substituted C₁₋₄alkyl group. Such preferred compounds may be prepared in a stepwise manner from a compound of formula (I) wherein Y is, for example, -CH₂OH-.

15

Thus, the hydroxy compound is first treated with dibenzoyloxydiethylaminophosphine in a suitable solvent such as tetrahydrofuran, preferably in the presence of an acid catalyst such as

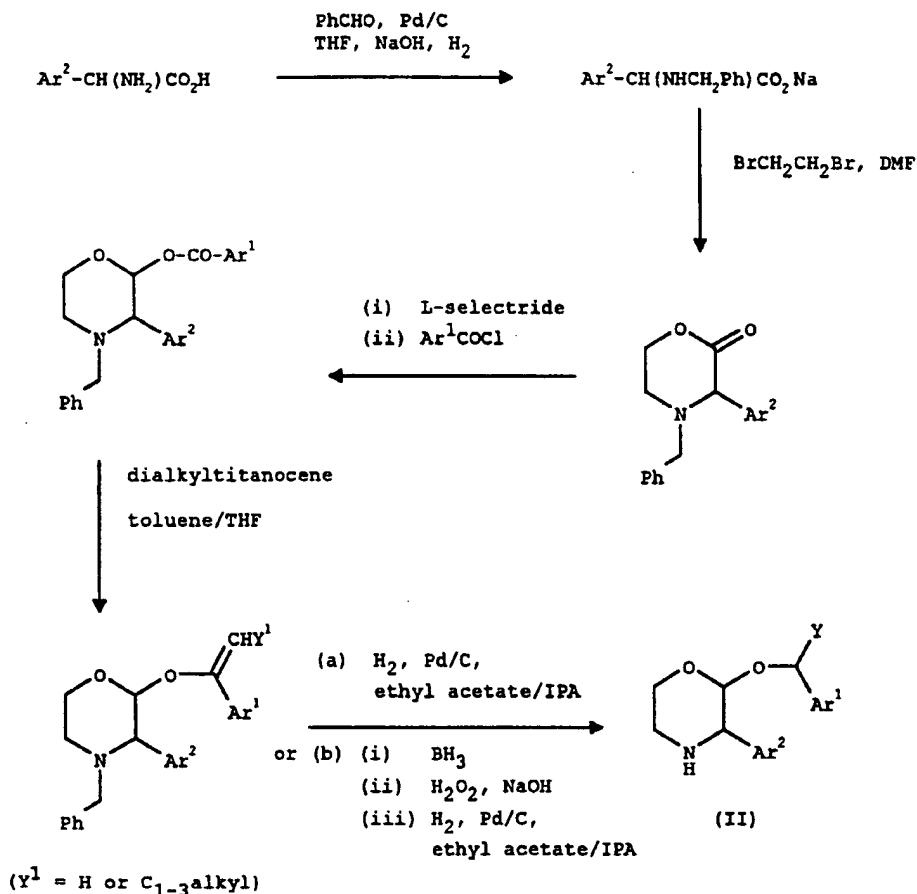
20

tetrazole. The resultant compound ($Y = \text{CH}_2\text{OP}(\text{OCH}_2\text{Ph})_2$) is then oxidised using, for example, 4-methylmorpholine-N-oxide to give the dibenzyl-protected phosphate. Deprotection by catalytic hydrogenation or transfer hydrogenation (palladium catalyst on carbon and ammonium
5 formate), in a suitable solvent such as methanol at reflux, yields the desired phosphate prodrug which may be converted to any desired salt form by conventional methodology.

In an alternative two-step method, the hydroxy compound of formula (I) may be reacted with a suitable base such as sodium hydride in
10 tetrahydrofuran, and tetrabenzylpyrophosphate added to yield the dibenzyl-protected phosphate which may be deprotected as described above.

The compounds of the formula (II), wherein A is $-\text{CH}_2-$, may be prepared by methods known in the art, for example as described in
15 European patent specification No. 0 528 495-A, published 24th February 1993.

The compounds of the formula (II), wherein A is $-\text{O}-$, may be prepared as shown in the following Scheme in which Ar^1 represents the R^1 , R^2 , R^3 substituted phenyl group; Ar^2 represents the R^4 , R^5 substituted
20 phenyl group and Ph represents phenyl:



L-Selectride is lithium tri-sec-butylborohydride.

The following references describe methods which may be applied by the skilled worker to the chemical synthesis set forth above once the

5 skilled worker has read the disclosure herein:

- (i) D.A. Evans *et al.*, *J. Am. Chem. Soc.*, (1990) 112, 4011.
- (ii) I. Yanagisawa *et al.*, *J. Med. Chem.*, (1984) 27, 849.
- (iii) R. Duschinsky *et al.*, *J. Am. Chem. Soc.*, (1948) 70, 657.
- (iv) F.N. Tebbe *et al.*, *J. Am. Chem. Soc.*, (1978) 100, 3611.
- (v) N.A. Petasis *et al.*, *J. Am. Chem. Soc.*, (1990) 112, 6532.
- (vi) K. Takai *et al.*, *J. Org. Chem.*, (1987) 52, 4412.

10 The Examples disclosed herein produce predominantly the preferred isomers. The unfavoured isomers are also produced as minor components. If desired they may be isolated and employed to prepare the

various stereoisomers in conventional manner, for example chromatography using an appropriate column. However, the skilled worker will appreciate that although the Examples have been optimized to the production of the preferred isomers, variation in solvent, reagents, chromatography etc can be readily employed to yield the other isomers.

It will be appreciated that compounds of the formula (I) wherein R⁶ contains an =O or =S substituent can exist in tautomeric forms. All such tautomeric forms and mixtures thereof are included within this invention. Most aptly the =O or =S substituent in R⁶ is the =O substituent.

Where they are not commercially available, the intermediates of formula (III) above may be prepared by the procedures described in the accompanying Examples or by alternative procedures which will be readily apparent to one skilled in the art.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The exemplified compounds of this invention were tested by the methods set out at pages 36 to 39 of International Patent Specification No. WO 93/01165. The compounds or, in the case of prodrugs, the parent compounds, were found to be active with IC₅₀ at the NK₁ receptor of less than 100nM on said test method.

The following non-limiting Examples further illustrate the present invention:

DESCRIPTION 1

[2S,3S]-1-tert-Butoxycarbonyl-2-phenyl-3-[(5-bromobenzofuran-7-yl)methyloxy]piperidine

5 (i) 4-Bromo-1-[(2,2-dimethoxyethyl)oxy]-2-methylbenzene

Bromoacetaldehyde dimethylacetal (6.05ml) was added to a stirred solution of 4-bromo-2-methylphenol (10.0g) and KOH (5.0g) in dry DMSO (40ml). The solution was warmed to 100°C for 4 hours. After this time the reaction mixture was cooled to room temperature and poured into water
10 (200ml). The aqueous layer was extracted with ether (2x100ml). The combined organic layers were separated, washed with 2N aqueous NaOH (2x50ml), dried over MgSO₄, filtered, and the solvent removed under reduced pressure to afford a brown oil. Purification by MPLC (15% ethyl acetate/n-hexane) afforded 4-bromo-1-[(2,2-dimethoxyethyl)oxy]-2-
15 methylbenzene as a colourless oil (6.24g). ¹H NMR (360MHz, CDCl₃) δ 2.21 (3H, s), 3.46 (6H, s), 3.98 (2H, d, J=3.6Hz), 4.69 (1H, t, J=3.6Hz), 6.56 (1H, d, J=7.2Hz), 7.26 (1H, d, J=7.2Hz), 7.39 (1H, s).

(ii) 5-Bromo-7-methyl-benzofuran

20 Polyphosphoric acid (2.0g) was added to a solution of 4-bromo-1-[(2,2-dimethoxyethyl)oxy]-2-methylbenzene (6.24g) in toluene (100ml) and the resulting mixture was warmed to reflux for 4 hours. The reaction mixture was cooled to room temperature and the supernatant organic layer decanted off. The black residue was basified with 2N aqueous
25 Na₂CO₃ and extracted with ethyl acetate (100ml). The organic layers were combined, washed with brine (2x100ml), dried over MgSO₄, filtered, and the solvent removed under reduced pressure. Purification by MPLC (2% ethyl acetate/n-hexane) gave 5-bromo-7-methyl-benzofuran as a colourless oil (2.77g). ¹H NMR (360MHz, CDCl₃) δ 2.48 (3H, s), 6.68 (1H, d, J=3.6Hz),
30 7.13 (1H, s), 7.53 (1H, s), 7.60 (1H, d, J=3.6Hz).

iii) 5-Bromo-7-bromomethyl Benzofuran

N-Bromosuccinimide (10.0g) and di-benzoylperoxide (500mg) were added in five equal portions to a solution of 5-bromo-7-methylbenzofuran (9.7g) stirring at reflux in CCl₄ (100ml), whilst being irradiated with an
5 850W lamp. After the final addition, the reaction was stirred at reflux for a further 2 hours, then cooled to room temperature. The solution was filtered and the filtrate washed with 2N NaOH-H₂O (40ml), brine (40ml), dried over MgSO₄, filtered and the solvent removed under reduced pressure. Purification by MPLC (1% ethyl acetate/n-hexane) gave
10 *5-bromo-7-bromomethyl benzofuran* as a clear oil (4.2g). ¹H NMR (360MHz, CDCl₃) δ 4.86 (2H, s), 6.69 (1H, d, J=3.0Hz), 7.54 (1H, s), 7.62 (1H, s), 7.86 (1H, d, J=3.0Hz).

15 (iv) [2S,3S]-1-tert-Butoxycarbonyl-2-phenyl-3-[(5-bromobenzofuran-7-yl)methyloxy]piperidine

Potassium bis(trimethylsilyl)amide (300mg) was added to a stirred solution of [2S,3S]-N-tert-butoxycarbonyl-2-phenylpiperidine-3-ol (160mg) in dry 1,2-dimethoxyethane (3.0ml) under a dry nitrogen atmosphere. After 30 minutes 5-bromo-7-bromomethylbenzofuran (290mg) was added,
20 and the reaction stirred for 18 hours at room temperature. The resulting mixture was then diluted with water (50ml), and extracted into ethyl acetate (2x50ml). The organic layers were separated and washed with brine (20ml), dried over MgSO₄, filtered and the solvent removed under reduced pressure. Purification by MPLC (20% ethyl acetate/n-hexane),
25 afforded [2S,3S]-1-tert-butoxycarbonyl-2-phenyl-3-[(5-bromobenzofuran-7-yl)methyloxy]piperidine as a yellow gum (136mg). ¹H NMR (360MHz, CDCl₃) δ 1.43 (9H, s), 1.65 (2H, m), 1.92 (2H, m), 2.70 (1H, t d, J=7.2, 3.0Hz), 3.74 (2H, m), 4.90 (2H, d, J=5.0Hz), 5.74 (1H, br s), 6.71 (1H, d, J=1.0Hz), 7.30-7.42 (4H, m), 7.58 (3H, m), 7.75 (1H, d, J=1.0Hz); MS
30 m/z CI⁺ 487 (M+H⁺).

DESCRIPTION 2

1-Methyl-5-tributylstannanyl-1H-[1,2,3]triazole

A solution of 1-methyl-1H-[1,2,3]triazole (350mg) in dry tetrahydrofuran (5.0ml) was added dropwise under nitrogen to a stirred, cooled (-78°C) solution of n-butyl lithium (2.81ml of 1.6M solution in hexanes) in dry tetrahydrofuran (10ml). After 1 hour tributylchlorostannane (1.46g) was added. The reaction was maintained at -78°C for 30min. and then allowed to warm to room temperature over 2 hours. The reaction mixture was diluted with brine (10ml) and extracted into ethyl acetate (50ml). The organic layer was separated, washed with brine (50ml), dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (20% ethyl acetate/n-hexane), to give *1-methyl-5-tributylstannanyl-1H-[1,2,3]triazole* as a yellow oil (1.03g). ¹H NMR (360MHz, CDCl₃) δ 0.87 (9H, m), 1.15 (6H, m), 1.28 (6H, m), 1.36 (6H, m), 4.02 (3H, s), 7.60 (1H, s); MS m/z CI⁺ 372 (M+H⁺).

DESCRIPTION 3

[2S,3S]-2-Phenyl-3-[[5-(1-methyl-1H-[1,2,3]triazol-5-yl)benzofuran-7-yl]methyloxy]piperidine hydrochloride

(i) [2S,3S]-1-tert-Butoxycarbonyl-2-phenyl-3-[[5-(1-methyl-1H-[1,2,3]triazol-5-yl)benzofuran-7-yl]-methyloxy]piperidine

Bis(triphenylphosphine)palladium dichloride (5.0mg) was added to a degassed solution of [2S,3S]-1-tert-butoxycarbonyl-2-phenyl-3-[(5-bromobenzofuran-7-yl)methyloxy]piperidine (111mg), and 1-methyl-5-tributylstannanyl-1H-[1,2,3]triazole (165mg) in dry toluene (5.0ml) under a dry nitrogen atmosphere. The resulting solution was warmed to reflux for 18 hours. After this time the reaction was cooled to room temperature and the solvent removed under reduced pressure. The residue was partitioned between aqueous NaHCO₃ solution (10ml, sat) and ethyl

acetate. The organic layer was washed with brine (10ml), dried over MgSO₄, filtered and the solvent removed under pressure. Purification by MPLC (1:1 ethyl acetate/n-hexane) afforded [2*S*,3*S*]-1-*tert*-butoxycarbonyl-2-phenyl-3-[[5-(1-methyl-1*H*-[1,2,3]triazol-5-yl)benzofuran-7-

5 yl)methyloxy]piperidine as a yellow foam (51mg). ¹H NMR (360MHz, CDCl₃) δ 1.45 (9H, s), 1.51-1.83 (5H, m), 2.73 (1H, t d, J=7.0, 3.0Hz), 3.94 (1H, m), 3.96 (3H, s), 5.02 (2H, d, J=1.0Hz), 5.76 (1H, br s), 6.84 (1H, d, J=1.0Hz), 7.26 (4H, m), 7.55 (3H, m), 7.70 (2H, br s); MS m/z Cl⁺ 489 (M+H⁺).

10

(ii) [2*S*,3*S*]-2-Phenyl-3-[[5-(1-methyl-1*H*-[1,2,3]triazol-5-yl)benzofuran-7-yl)methyloxy]piperidine hydrochloride

A solution of HCl in ethanol (2ml, 5N) was added to a stirred solution of [2*S*,3*S*]-1-*tert*-butoxycarbonyl-2-phenyl-3-[[5-(1-methyl-1*H*-
15 [1,2,3]triazol-5-yl)benzofuran-7-yl)methyloxy]piperidine (51mg) in dry ethanol. After 2 hours the solvent was removed under reduced pressure and the residue was recrystallised from ether/ethanol to afford [2*S*,3*S*]-2-phenyl-3-[[5-(1-methyl-1*H*-[1,2,3]triazol-5-yl)benzofuran-7-yl)methyloxy]piperidine hydrochloride as white needles (12.2mg), mp 126-
20 127°C. ¹H NMR (360MHz, D₂O) δ 1.65-1.80 (2H, m), 2.20 (1H, m), 2.40 (1H, m), 3.21 (1H, m), 3.63 (1H, m), 3.92 (3H, s), 3.96 (1H, br s), 4.39 (1H, br s), 4.66 (1H, d, J=11.0Hz), 4.94 (1H, d, J=11.0Hz), 6.70 (1H, d, J=1.0Hz), 6.90 (1H, d, J=1.0Hz), 7.05-7.16 (5H, m), 7.60 (1H, d, J=1.0Hz), 7.73 (1H, s), 7.78 (1H, d, J=1.0Hz); MS m/z Cl⁺ 389 (M+H⁺).

25

EXAMPLE 1

[2*S*,3*S*]-1-[[5-(Dimethylaminomethyl)-1*H*-[1,2,3]triazol-4-yl)methyl]-2-phenyl-3-[[5-(1-methyl-1*H*-[1,2,3]triazol-5-yl)benzofuran-7-yl)methyloxy]piperidine hydrochloride

30

(i) [2S,3S]-1-(4-Chlorobut-2-yn-1-yl)-2-phenyl-3-[(5-(1-methyl-1H-[1,2,3]triazol-5-yl)benzofuran-7-yl)methyloxy]piperidine

A solution of [2S,3S]-2-phenyl-3-[(5-(1-methyl-1H-[1,2,3]triazol-5-yl)benzofuran-7-yl)methyloxy]piperidine hydrochloride (230mg) in
5 N,N-dimethylformamide (2ml) was slowly added to a solution of
1,4-dichlorobut-2-yne (106ml) and potassium carbonate (224mg) in
N,N-dimethylformamide (2.0ml). The solution was stirred for 18 hours at
room temperature and the solvent removed under reduced pressure. To
the residue was added water (40ml) and the product was extracted with
10 ethyl acetate (3x10ml). The combined organic fractions were washed with
water, saturated brine, dried over MgSO₄, filtered and the solvent
removed under reduced pressure. The residue was purified by MPLC
(10% ethyl acetate/hexane) to give [2S,3S]-1-(4-chlorobut-2-yn-1-yl)-2-
phenyl-3-[(5-(1-methyl-1H-[1,2,3]triazol-5-yl)benzofuran-7-
15 yl)methyloxy]piperidine as a yellow oil (205mg). ¹H NMR (360MHz, CDCl₃)
δ 1.57 (2H, m), 2.22 (2H, m), 2.98 (1H, m), 3.27 (2H, d, J=3.0Hz), 3.43
(1H, br s), 3.62 (1H, br s), 3.95 (3H, s), 4.13 (2H, s), 4.46 (1H, d, J=11.0Hz),
4.82 (2H, d, J=11.0Hz), 6.77 (1H, d, J=1.0Hz), 6.87 (1H, s), 7.15 (3H, m),
7.38 (2H, m), 7.43 (1H, s), 7.62 (2H, br s); MS m/z (CI⁺) 475 (M+H⁺).

20 ii) [2S,3S]-1-(4-Azidobut-2-yn-1-yl)-2-phenyl-3-[(5-(1-methyl-1H-[1,2,3]triazol-5-yl)benzofuran-7-yl)methyloxy]piperidine

To a solution of [2S,3S]-1-(4-chlorobut-2-yn-1-yl)-2-phenyl-3-[(5-(1-
methyl-1H-[1,2,3]triazol-5-yl)benzofuran-7-yl)methyloxy]piperidine
25 (205mg) in dimethyl sulfoxide (3.0ml) was added sodium azide (32.5mg).
The solution was stirred for 20 hours at room temperature at which time
aqueous ammonium chloride and ethyl acetate were added. The organic
phase was separated, washed with water (20ml), saturated brine (20ml)
dried over MgSO₄, filtered and the solvent removed under reduced
30 pressure to give [2S,3S]-1-(4-azidobut-2-yn-1-yl)-2-phenyl-3-[(5-(1-methyl-
1H-[1,2,3]triazol-5-yl)benzofuran-7-yl)methyloxy]piperidine as a white

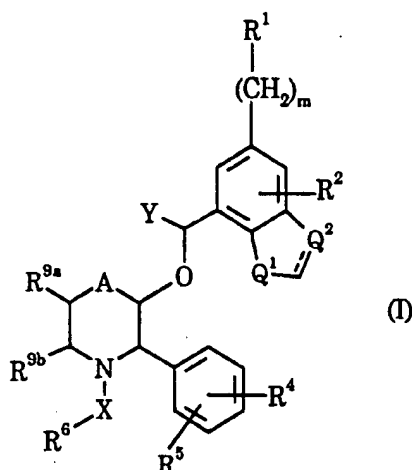
solid (120mg). ¹H NMR (360MHz, CDCl₃) δ 1.20-1.60 (2H, m), 2.22 (2H, m), 2.67 (1H, m), 2.98 (1H, m), 3.27 (2H, m), 3.47 (1H, br s), 3.62 (1H, br s), 3.91 (2H, s), 3.95 (3H, s), 4.47 (1H, d, J=11.0Hz), 4.81 (1H, d, J=11.0Hz), 6.77 (1H, d, J=1.0Hz), 6.87 (1H, s), 7.15 (3H, m), 7.38 (2H, m), 7.43 (1H, s), 7.62 (2H, br s); MS m/z (CI⁺) 482 (M+H⁺).

iii) [2S,3S]-1-[(5-(Dimethylaminomethyl)-1H-[1,2,3]triazol-4-yl)methyl]-2-phenyl-3-[(5-(1-methyl-1H-[1,2,3]triazol-5-yl)benzofuran-7-yl)methyloxy]piperidine hydrochloride

Dimethylamine (approximately 10ml) was condensed at -80°C in a pressure tube and to this was added a solution of [2S,3S]-1-(4-azidobut-2-yn-1-yl)-2-phenyl-3-[(5-(1-methyl-1H-[1,2,3]triazol-5-yl)benzofuran-7-yl)methyloxy]piperidine (120mg) in dioxan (5ml). The tube was sealed and the solution was heated at 80°C for 14 hours. The solvent was evaporated under reduced pressure to dryness and the residue was purified by MPLC [5% methanol in dichloromethane containing 0.25% ammonia (SG. 0.88)] to give [2S,3S]-1-[(5-dimethylaminomethyl)-1H-[1,2,3]-triazol-4-yl)methyl]-2-phenyl-3-[(5-(1-methyl-1H-[1,2,3]triazol-5-yl)benzofuran-7-yl)methyloxy]piperidine as a clear oil (47mg). To a solution of this residue in diethyl ether was added 5M-HCl in ethanol. The solution was evaporated to dryness and the residue recrystallised from ether/ethanol to give [2S,3S]-1-[(5-(Dimethylaminomethyl)-1H-[1,2,3]triazol-4-yl)methyl]-2-phenyl-3-[(5-(1-methyl-1H-[1,2,3]triazol-5-yl)benzofuran-7-yl)methyloxy]piperidine hydrochloride (57mg) mp 136-138°C. ¹H NMR (360MHz, D₂O) δ 1.64 (1H, m), 1.87 (1H, m), 2.34 (2H, m), 2.65 (6H, s), 3.27 (1H, d, J=14.0Hz), 3.71-3.78 (3H, m), 3.85 (1H, br s), 3.93 (3H, s), 4.24 (1H, s), 4.33 (1H, d, J=16.0Hz), 4.38 (1H, d, J=16.0Hz), 4.69 (1H, d, J=14.0Hz), 5.00 (1H, d, J=14.0Hz), 6.79 (1H, s), 6.92 (1H, d, J=1.0Hz), 7.16 (5H, m), 7.63 (1H, s), 7.74 (1H, s), 7.81 (1H, d, J=1.0Hz); m/z (CI⁺) 527 (M+H⁺).

CLAIMS:

1. A compound of the formula (I):



- 5 wherein

R¹ is phenyl or a 5- or 6-membered aromatic heterocyclic group containing 1, 2, 3 or 4 heteroatoms, selected from nitrogen, oxygen and sulphur, which aryl or heteroaryl group is optionally substituted by one or two substituents selected from halogen, C₁₋₆alkyl, C₁₋₆alkoxy, CF₃, OCF₃,
 10 NO₂, CN, SR^a, SOR^a, SO₂R^a, COR^a, CO₂R^a, (CH₂)_nCONR^aR^b, (CH₂)_nNR^aR^b or (CH₂)_nNR^aCOR^b, where R^a and R^b are independently hydrogen or C₁₋₄alkyl and n is zero, 1 or 2;

R² is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆alkoxy, CF₃, OCF₃, NO₂, CN, SR^a, SOR^a, SO₂R^a, CO₂R^a, CONR^aR^b, C₂₋₆alkenyl, C₂₋₆alkynyl or C₁₋₄alkyl
 15 substituted by C₁₋₄alkoxy, where R^a and R^b each independently represent hydrogen or C₁₋₄alkyl;

R⁴ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆alkoxy, CF₃, NO₂, CN, SR^a, SOR^a, SO₂R^a, CO₂R^a, CONR^aR^b, C₂₋₆alkenyl, C₂₋₆alkynyl or C₁₋₄alkyl substituted by C₁₋₄alkoxy, where R^a and R^b each independently represent
 20 hydrogen or C₁₋₄alkyl;

R⁵ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆alkoxy substituted by C₁₋₄alkoxy or CF₃;

R⁶ is a 5-membered or 6-membered heterocyclic ring containing 2 or 3 nitrogen atoms optionally substituted by =O, =S or a C₁₋₄alkyl group, and optionally substituted by a group of the formula ZNR⁷R⁸ where

Z is C₁₋₆alkylene or C₃₋₆cycloalkylene;

5 R⁷ is hydrogen, C₁₋₄alkyl, C₃₋₇cycloalkyl or C₃₋₇cycloalkylC₁₋₄alkyl, or C₂₋₄alkyl substituted by C₁₋₄alkoxy or hydroxyl;

R⁸ is hydrogen, C₁₋₄alkyl, C₃₋₇cycloalkyl or C₃₋₇cycloalkylC₁₋₄alkyl, or C₂₋₄alkyl substituted by one or two substituents selected from C₁₋₄alkoxy, hydroxyl or a 4, 5 or 6 membered heteroaliphatic ring containing one or
10 two heteroatoms selected from N, O and S;

or R⁷, R⁸ and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by one or two groups selected from hydroxy or C₁₋₄alkyl optionally substituted by a C₁₋₄alkoxy or hydroxyl group, and optionally containing a double bond,
15 which ring may optionally contain an oxygen or sulphur ring atom, a group S(O) or S(O)₂ or a second nitrogen atom which will be part of a NH or NR^c moiety where R^c is C₁₋₄alkyl optionally substituted by hydroxy or C₁₋₄alkoxy;

or R⁷, R⁸ and the nitrogen atom to which they are attached form a
20 non-aromatic azabicyclic ring system of 6 to 12 ring atoms;

or Z, R⁷ and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms which may optionally contain an oxygen ring atom;

R^{9a} and R^{9b} are each independently hydrogen or C₁₋₄alkyl, or R^{9a} and
25 R^{9b} are joined so, together with the carbon atoms to which they are attached, there is formed a C₅₋₇ ring;

the dotted line is an optional double bond;

A is -O- or -CH₂-;

Q¹ is oxygen, sulphur or -NH-;

30 Q² is -N=, -NH-, -CH= or -CH₂-;

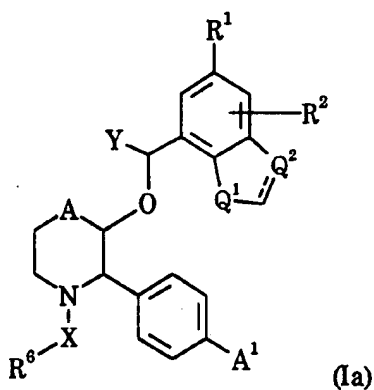
X is an alkylene chain of 1 to 4 carbon atoms optionally substituted by oxo;

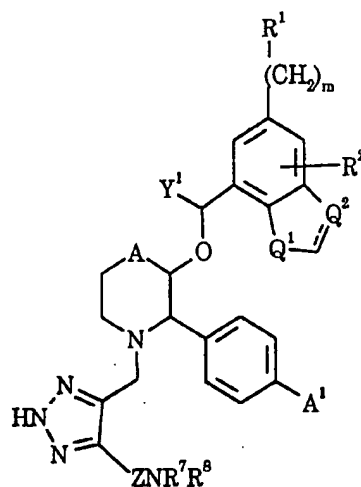
Y is hydrogen or a C₁₋₄alkyl group optionally substituted by a hydroxyl group; and

5 m is zero or 1;

or a pharmaceutically acceptable salt and prodrug thereof.

2. A compound as claimed in claim 1 of the formula (Ia) or a pharmaceutically acceptable salt or prodrug thereof:



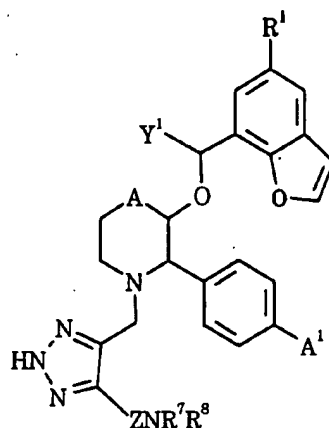


(Ib)

wherein A, Z, R¹, R², R⁷, R⁸, Q¹, Q², the dotted line and m are as defined in claim 1, A¹ is fluorine or hydrogen and Y¹ is hydrogen or methyl.

5

4. A compound as claimed in of claim 1 of the formula (Ic) or a pharmaceutically acceptable salt thereof:

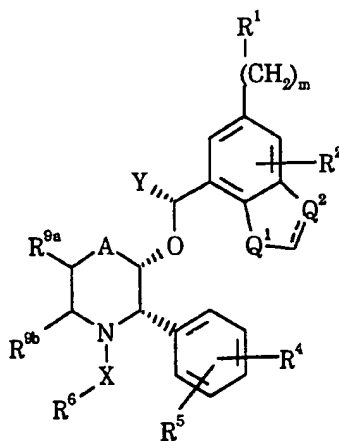


(Ic)

10

wherein R¹, R⁷, R⁸ and Z are as defined in claim 3, A¹ is fluorine or hydrogen and Y¹ is hydrogen or methyl.

5. A compound as claimed in claim 1 of the formula (Id) or a pharmaceutically acceptable salt or prodrug thereof:



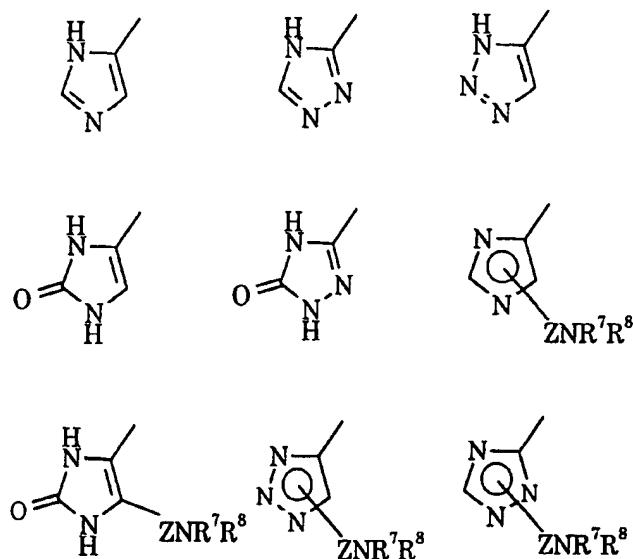
(Id)

5

wherein A, X, Y, Q¹, Q², R¹, R², R⁴, R⁵, R⁶, R^{9a}, R^{9b}, m and the dotted line are as defined in claim 1.

10 6. A compound as claimed in claim 1 wherein X represents CH₂, CH(CH₃) or CH₂CH₂.

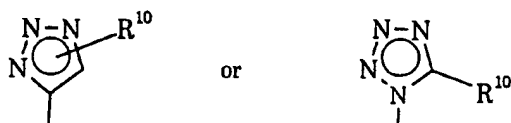
7. A compound as claimed in claim 1 wherein R⁶ represents a heterocyclic ring selected from:



wherein Z, R⁷ and R⁸ are as defined in claim 1.

- 5 8. A compound as claimed in any one of claims 1 to 7 wherein Z is CH₂ or CH₂CH₂ and NR⁷R⁸ is amino, methylamino, dimethylamino, diethylamino, azetidiny, pyrrolidino and morpholino.

9. A compound as claimed in any one of claims 1 to 8 wherein R¹
10 is the group



- where R¹⁰ is halogen, C₁₋₆alkyl, C₁₋₆alkoxy, CF₃, OCF₃, NO₂, CN, SR^a,
15 SOR^a, SO₂R^a, COR^a, CO₂R^a, (CH₂)_nCONR^aR^b, (CH₂)_nNR^aR^b or
(CH₂)_nNR^aCOR^b, where R^a and R^b are hydrogen or C₁₋₄alkyl, and n is zero,
1 or 2.

10. A compound as claimed in claim 1 wherein Q¹ is an oxygen atom, Q² is -CH= or -CH₂-, and the dotted line represents a double bond.

11. A compound selected from:

- 5 [2S,3S]-1-[(5-(dimethylaminomethyl)-1H-[1,2,3]triazol-4-yl)methyl]-2-phenyl-3-[[5-(1-methyl-1H-1,2,3-triazol-5-yl)benzofuran-7-yl]methoxy]piperidine;
[2S,3S]-1-[(5-(dimethylaminomethyl)-1H-[1,2,3]triazol-4-yl)methyl]-2-phenyl-3-[(5-(5-methyl-1H-tetrazol-1-yl)benzofuran-7-yl)methoxy]
10 piperidine;
or a pharmaceutically acceptable salt or prodrug thereof.

12. A compound as claimed in any preceding claim for use in therapy.

15

13. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 11 in association with a pharmaceutically acceptable carrier or excipient.

20

14. A method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, or a composition comprising a
25 compound according to claim 1, or a pharmaceutically acceptable salt thereof.

15. A method according to claim 14 for the treatment or prevention of pain or inflammation.

30

16. A method according to claim 14 for the treatment or prevention of migraine.

17. A method according to claim 14 for the treatment or
5 prevention of emesis.

18. A method according to claim 14 for the treatment or prevention of postherpetic neuralgia.

10 19. The use of a compound as claimed in any one of claims 1 to 11 for the manufacture of a medicament for the treatment or prevention of a physiological disorder associated with an excess of tachykinins.

20 20. The use of a compound as claimed in any one of claims 1 to 11 for the manufacture of a medicament for the treatment or prevention of pain or inflammation.

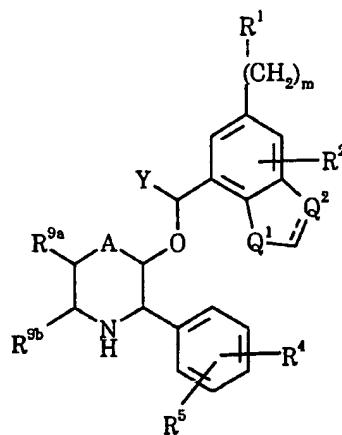
20 21. The use of a compound as claimed in any one of claims 1 to 11 for the manufacture of a medicament for the treatment or prevention of migraine.

25 22. The use of a compound as claimed in any one of claims 1 to 11 for the manufacture of a medicament for the treatment or prevention of emesis.

23. The use of a compound as claimed in any one of claims 1 to 11 for the manufacture of a medicament for the treatment or prevention of postherpetic neuralgia.

30 24. A process for the preparation of a compound as claimed in claim 1 which comprises:

(A) reaction of a compound of formula (II)



(II)

5

wherein R¹, R², R⁴, R⁵, R^{9a}, R^{9b}, A, Y, Q¹, Q², the dotted line and m are as defined in claim 1, with a compound of formula (III):

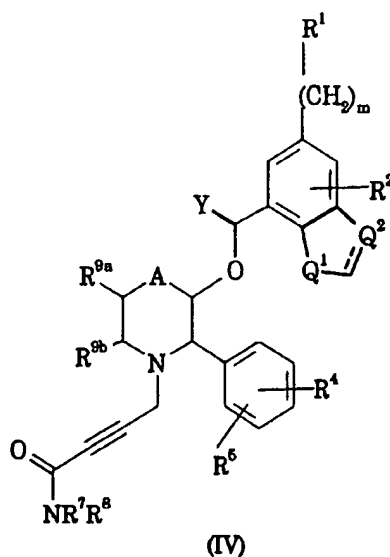


10

where X is as defined in claim 1, R^{6a} is a group of the formula R⁶ as defined in claim 1 or a precursor thereof and X¹ is a leaving group; and, if R^{6a} is a precursor group, converting it to a group R⁶; or

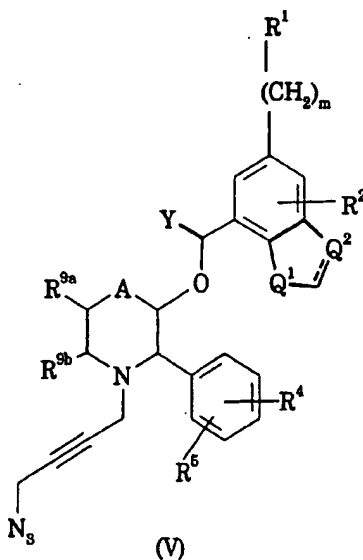
15

(B), for compounds of formula (I) wherein R⁶ represents 1,2,3-triazol-4-yl substituted by CH₂NR⁷R⁸, and X is -CH₂-, reaction of a compound of formula (IV)



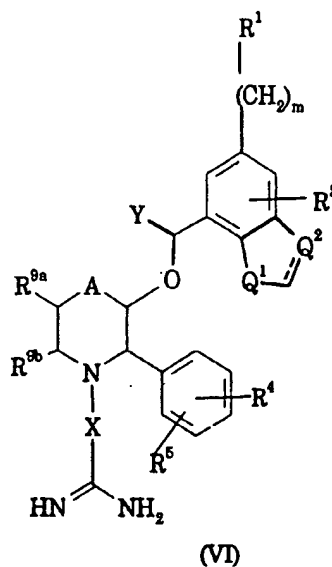
with an azide, followed by reduction of the carbonyl group adjacent to $\text{-NR}^7\text{R}^8$ using a suitable reducing agent; or

- 5 (C), for compounds of formula (I) wherein R^6 represents 1,2,3-triazol-4-yl substituted by $\text{CH}_2\text{NR}^7\text{R}^8$, and X is $\text{-CH}_2\text{-}$, reaction of a compound of formula (V)



with an amine of formula NHR^7R^8 ; or

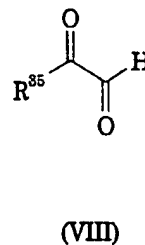
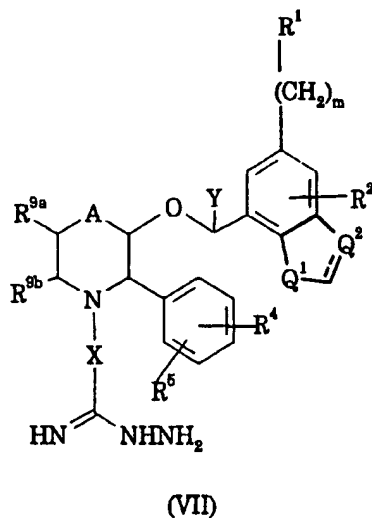
(D), for compounds of formula (I) wherein R^6 represents substituted or unsubstituted 1,3,5-triazine, reaction of intermediates of formula (VI):



with substituted or unsubstituted 1,3,5-triazine; or

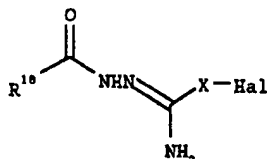
5

(E), for compounds of formula (I) wherein R^6 represents substituted or unsubstituted 1,2,4-triazine, reaction of an intermediate of formula (VII) with a dicarbonyl compound of formula (VIII):



10 wherein R^{35} represents H or a suitable substituent such as ZNR^7R^8 ; or

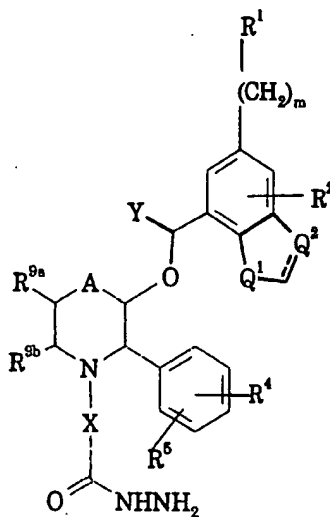
(F), for compounds of formula (I) wherein R^8 represents a substituted 1,2,4-triazolyl group, reaction of an intermediate of formula (II) with a compound of formula (IX)



(IX)

5 wherein X is as defined in claim 1, Hal is a halogen atom, and R^{18} is H, CONH_2 or OCH_3 (which is converted to an oxo substituent under the reaction conditions), in the presence of a base, followed where necessary by conversion to a compound of formula (I); or

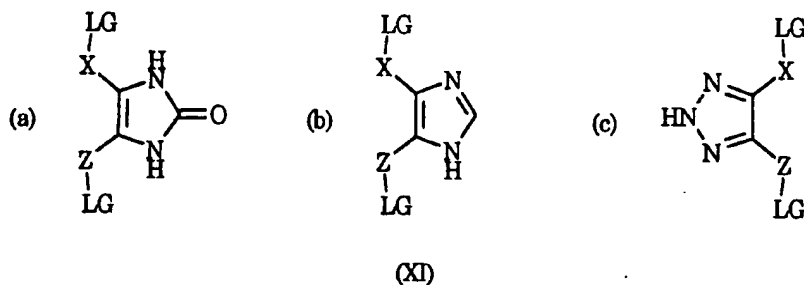
10 (G), for compounds of formula (I) wherein R^8 represents thioxotriazolyl, reaction of an intermediate of formula (X)



(X)

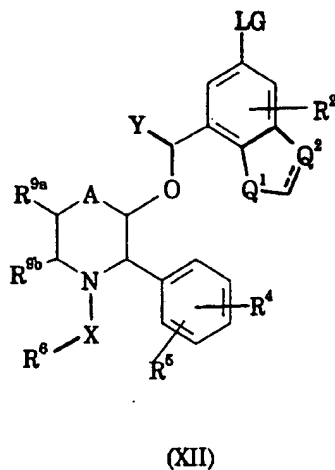
with a compound of formula HNCS , in the presence of a base; or

15 (H), for compounds of formula (I) wherein the heterocycle R^8 is substituted by ZNR^7R^8 , reaction of an intermediate of formula (II) as defined above with one of the compounds of formula (XI):



wherein each LG, which may be the same or different, is a leaving group,
 5 and X and Z are as defined in claim 1, followed by reaction of the resultant compound with an amine NHR^7R^8 to complete the ZNR^7R^8 moiety; or

(J), reaction of intermediates of formula (XII)



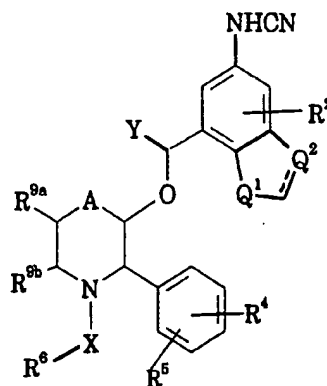
10

wherein LG is a leaving group, with a compound of formula (XIII)



15 wherein R^{40} is $\text{B}(\text{OH})_2$ or $\text{Sn}(\text{alkyl})_3$, in the presence of a palladium catalyst; or

(K), for compounds of formula (I) wherein R^1 is a tetrazol-1-yl group and m is zero, reaction of intermediates of formula (XIV)



(XIV)

5 with ammonium chloride and sodium azide at elevated temperature;

each process being followed, where necessary, by the removal of any protecting group where present;

and when the compound of formula (I) is obtained as a mixture of
 10 enantiomers or diastereoisomers, optionally resolving the mixture to obtain the desired enantiomer;

and/or, if desired, converting the resulting compound of formula (I) or a salt thereof, into a pharmaceutically acceptable salt or prodrug thereof.

15

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 96/01477

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D405/14 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | WO,A,94 19323 (MERCK SHARP & DOHME ;BAKER RAYMOND (GB); SWAIN CHRISTOPHER JOHN (G) 1 September 1994 see abstract; claim 3 --- | 1-24 |
| A | WO,A,95 06645 (GLAXO GROUP LTD ;NAYLOR ALAN (GB); EVANS BRIAN (GB)) 9 March 1995 cited in the application see abstract; claims --- | 1-24 |
| A | EP,A,0 577 394 (MERCK & CO INC) 5 January 1994 cited in the application see abstract; claims 5,7 ----- | 1-24 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

9 October 1996

Date of mailing of the international search report

18.10.96

Name and mailing address of the ISA

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Authorized officer

Paisdor, B

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB96/01477

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
ALTHOUGH CLAIMS 14-18 ARE DIRECTED TO A METHOD OF TREATMENT OF (DIAGNOSTIC METHOD PRACTISED ON) THE HUMAN/ANIMAL BODY THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOUND/COMPOSITION.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 96/01477

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| WO-A-9419323 | 01-09-94 | AU-A- 6109394 | 14-09-94 |
| | | CA-A- 2152925 | 01-09-94 |
| | | EP-A- 0683767 | 29-11-95 |
| | | JP-T- 8506823 | 23-07-96 |
| ----- | | | |
| WO-A-9506645 | 09-03-95 | AU-A- 7655094 | 22-03-95 |
| | | ZA-A- 9406470 | 14-11-95 |
| ----- | | | |
| EP-A-0577394 | 05-01-94 | AU-A- 4156893 | 06-01-94 |
| | | AU-A- 4656193 | 24-01-94 |
| | | BG-A- 99274 | 30-04-96 |
| | | CA-A- 2099233 | 30-12-93 |
| | | CN-A- 1087902 | 15-06-94 |
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| | | HR-A- 931003 | 28-02-95 |
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| | | JP-A- 6172178 | 21-06-94 |
| | | NO-A- 945064 | 28-02-95 |
| | | NZ-A- 254476 | 25-09-96 |
| | | SI-A- 9300346 | 31-12-93 |
| | | SK-A- 160094 | 11-07-95 |
| | | WO-A- 9400440 | 06-01-94 |
| | | AU-A- 4160893 | 06-01-94 |
| | | ZA-A- 9304624 | 20-06-94 |
| ----- | | | |